

## Original Article

# The efficacy of sulodexide combined with Jinshuibao for treating early diabetic nephropathy patients

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**Abstract:** Diabetic nephropathy (DN) is a common, serious and chronic complication of diabetes mellitus (DM). The early intervention and active treatment of DN can delay its occurrence and development effectively. Sulodexide is a glycosaminoglycan drug, and Jinshuibao is a fermented *Cordyceps sinensis* powder preparation. In our study, we used sulodexide capsules combined with Jinshuibao capsules to treat early DN. We found that sulodexide combined with Jinshuibao in the treatment of early DN can effectively reduce the formation of albuminuria, improve the hypercoagulability of renal microcirculation and fibrinolytic activity, improve vascular endothelial function, promote anti-inflammation reactions, and reduce oxidative stress. Combination therapy is significantly more effective than monotherapy, and it can delay the further progression of DN without increasing the adverse reactions.

**Keywords:** Early diabetic nephropathy, sulodexide, Jinshuibao, efficacy, albuminuria

## Introduction

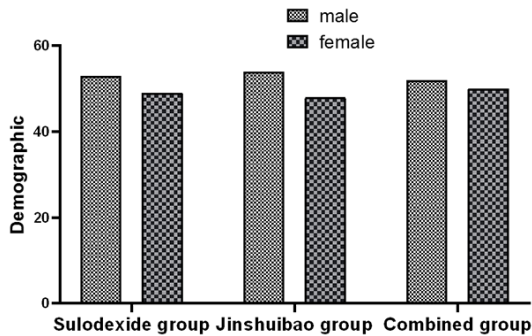
Changes in diet and lifestyle and the aging of the population in China have led to chronic non-communicable diseases becoming one of the greatest threats to human health. In recent years, the number of patients with diabetes mellitus (DM) has risen sharply. It is estimated that DM affects more than 450 million adults worldwide currently, and its prevalence is increasing yearly, with more than 640 million adults expected to suffer from DM by 2040 [1]. The number of DM patients has exceeded 100 million in China [2]. DM has become another important, chronic, non-communicable disease which seriously endangers human health in addition to cardiovascular and cerebrovascular diseases and cancer [3].

Long-term, poor glycemic control in DM patients may lead to chronic damage and dysfunction of the kidneys, retinas, blood vessels, nerves, etc., resulting in a series of chronic DM complications [4]. Among them, diabetic nephropathy (DN) is a serious DM microvascular complication, and it is one of the main causes of chronic

renal insufficiency and also an important cause of disability and death in DM patients. With the surge in the total number of DM patients, the incidence of DN has also increased significantly [5]. The early stage of DN mainly manifests as microalbuminuria. With the progress of the disease, different degrees of proteinuria and renal dysfunction may occur and even develop into end-stage nephropathy [6]. Therefore, it is of great significance to prevent and treat early DN actively and delay its progression.

In addition to stabilizing blood sugar and other basic treatments, DN treatment also includes controlling albuminuria, protecting the renal vascular endothelium, reducing renal vascular hypercoagulability, postponing glomerulosclerosis, promoting anti-inflammatory reactions, and reducing oxidative stress, etc. [7-9]. Currently, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are recognized as having the functions of clinically controlling albuminuria and postponing glomerulosclerosis. However, ACEI and ARBs are limited by patients' serum creatinine levels, which bring on certain limitations in their

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**Figure 1.** Gender data of the three groups.

clinical application [10, 11]. Therefore, one hot topic in DN treatment involves actively seeking new treatment options. In our study, the glycosaminoglycan drug sulodexide combined with the fermented *Cordyceps sinensis* powder preparation Jinshuibao were applied to treat early DN. The purpose of our study was to observe the clinical efficacy and safety of sulodexide capsules combined with Jinshuibao capsules in treating early-stage DN and to actively explore a more reasonable and effective DN therapeutic schedule.

### Materials and methods

#### Patients

306 early DN patients admitted to our hospital were enrolled in our study during the period March 2016 to October 2018. There were 150 males and 156 females. Their ages ranged from 42 to 75 years old, with an average age of  $(52.36 \pm 3.44)$  years old, and an average disease duration of  $(8.23 \pm 2.17)$  years. This research was approved by the ethics committee of our hospital. All the patients and their families were required to sign a written informed consent form. Inclusion criteria: Patients who met “the DM diagnostic criteria in the guidelines for the prevention and treatment of type 2 diabetes in China (2015 edition)”, patients diagnosed with type 2 diabetes, patients with a quantitative urinary albumin excretion rate (UAER) 20-200  $\mu\text{g}/\text{min}$ , and patients with a multiple 24 h urine protein quantitation 0.15-0.5 g/24 h. Exclusion criteria: Patients with primary nephropathy, other secondary nephropathy, or diseases that may lead to elevated albuminuria, patients with renal (creatinine, urea, uric acid) dysfunction, patients with serious

cardiovascular or cerebrovascular diseases, and patients with severe hemorrhages or coagulopathy, ketosis, fever, infection, etc.

#### Treatments

306 patients with early DN were randomly and equally divided into three groups, so each group had 102 patients. There were 53 males and 49 females in the sulodexide group, with an average age of  $(52.28 \pm 3.36)$  years old and an average disease duration of  $(8.16 \pm 2.08)$  years. There were 54 males and 48 females in the Jinshuibao group, with an average age of  $(52.43 \pm 3.41)$  years old and an average disease duration of  $(8.25 \pm 2.21)$  years. There were 52 males and 50 females in the combined group, with an average age of  $(52.45 \pm 3.48)$  years old and an average disease duration of  $(8.29 \pm 2.26)$  years. There were no significant differences in the general clinical data of the patients in the three groups ( $P > 0.05$ ), as shown in **Figure 1**. According to each patient's condition, the patients in the three groups were treated with oral hypoglycemic agents or a subcutaneous injection of insulin to control their blood sugar, and they were advised to consume a low-salt, low-fat, high-quality, low-protein diet, etc. In addition to this treatment, the patients in the sulodexide group were orally administered sulodexide soft capsules (250 LSU  $\times$  12 tablets/box, Alpha Weissman Pharmaceutical Co., Ltd., Italy), 250 LSU, and 2 times/day. The patients in the Jinshuibao group were orally administered Jinshuibao capsules (0.33 g  $\times$  72 tablets/box, Jimin Kexin Jinshuibao Pharmaceutical Co., Ltd, Jiangxi), 1.98 g, 3 times/day. The combined group patients were orally administered sulodexide soft capsules (250 LSU, 2 times/day) and Jinshuibao capsules (1.98 g, 3 times/day), for 8 weeks. During the course of treatment, 7 patients in the sulodexide group, 12 patients in the Jinshuibao group, and 9 patients in the combined group withdrew from the observational study.

#### Evaluation indicators

24-hour urine specimens were collected from each patient, and their 24 hour urine total protein (24 h-UTP) levels were determined using the biuret colorimetric method, and radioimmunoassays were used to measure their urine albumin content, and their UAER levels were calculated. The fibrinogen (FIB), plasminogen

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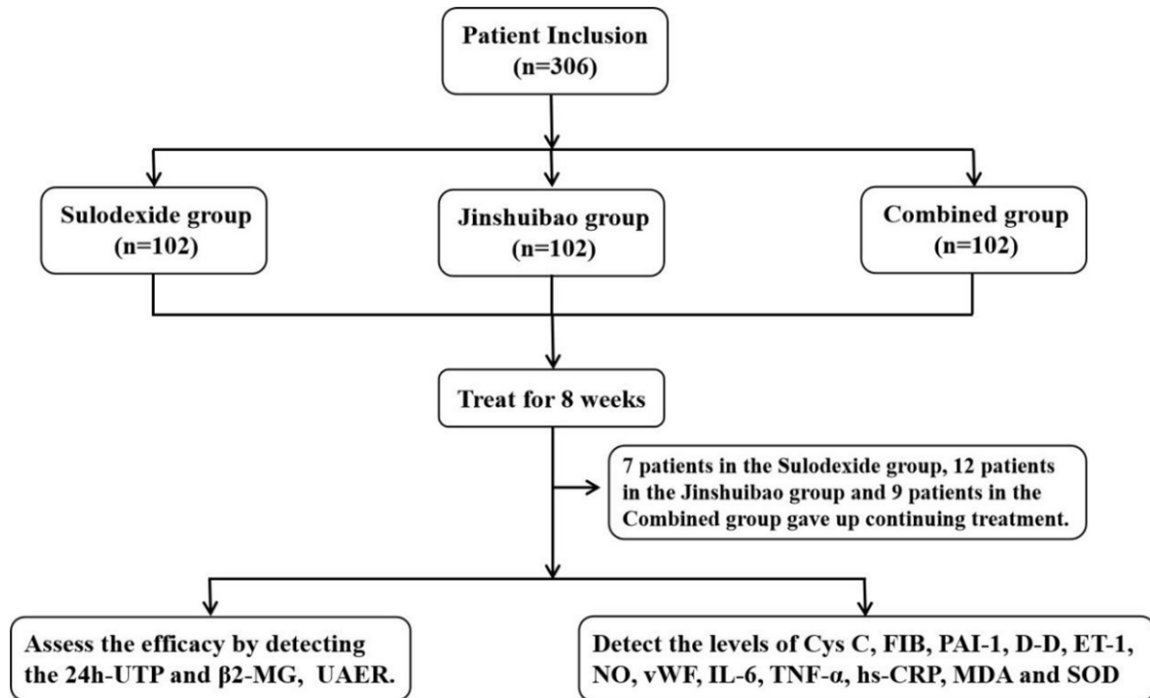


Figure 2. Experimental flowchart.

activator inhibitor 1 (PAI-1), and D-dimer (D-D) levels were determined using an automatic biochemical analyzer. The kits were provided by Beijing Leadman Biochemical Co., Ltd. (Beijing, China). Their serum malondialdehyde (MDA) and superoxide dismutase (SOD) levels were measured using thiobarbituric acid colorimetry. The endothelin-1 (ET-1) levels were measured using radioimmunoassays, and the nitrate reductase method was used to measure their nitric oxide (NO) levels. The urine  $\beta_2$  microglobulin ( $\beta_2$ -MG), cystatin C (Cys C), von Willebrand factor (vWF), interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and high-sensitivity c-reactive protein (hs-CRP) levels were quantified using ELISA kits. The kits were purchased from Beijing Dingguo Changsheng Biotechnology Co., Ltd. (Beijing, China). The experiment was carried out in strict accordance with the kit's instructions. After 8 weeks of treatment, the clinical effective rates of the three groups of patients were observed. The patients' symptoms improved significantly, and their 24 h-UTP, UAER, and  $\beta_2$ -MG levels decreased by more than 50% were declared to be prominently effective. The patients whose symptoms were reduced but did not meet the above indicators did not reach the standard of prominently effective but were considered improved.

The patients whose symptoms did not improve or even worsened and who did not meet the above indicators did not improve significantly and were defined as invalid. Effective rate = (Prominently effective number + Improvement number)/Total number  $\times$  100%. Some adverse drug reactions, such as gastrointestinal reactions, headache, bleeding gums, and abnormal liver function, etc., were recorded in the 3 groups of patients during the treatment. A flowchart of the experiment is shown in **Figure 2**.

### Statistical methods

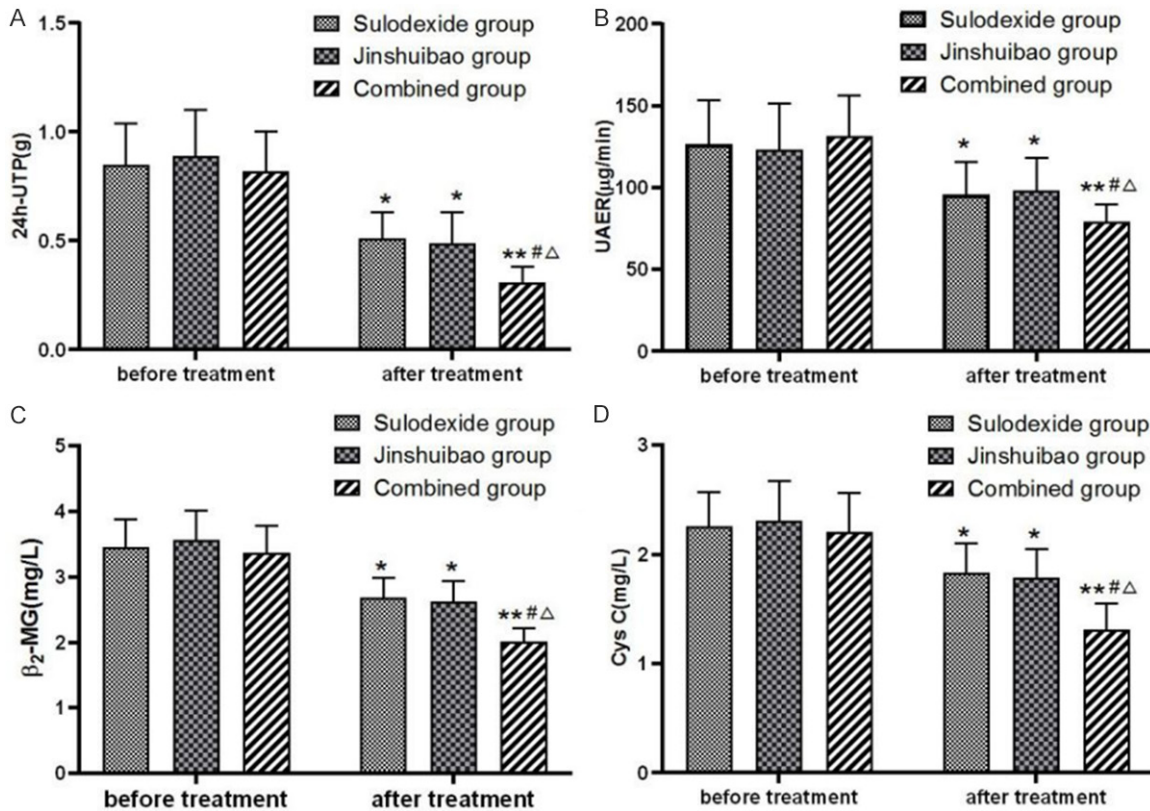
The data gathered in this experiment were statistically analyzed using SPSS 20.0 (SPSS Co., Ltd., Chicago, USA). The count data were expressed as (rate), and chi-square tests were used for the comparisons between groups. The measurement data were expressed as the (mean  $\pm$  standard deviation), and t tests were used for the comparisons between groups. One-way analyses of variance and LSD post hoc tests were used for the comparisons between multiple groups. *P* values less than 0.05 were considered to be statistically significant.

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**Table 1.** Comparison of the clinical efficacy [n (%)]

Groups	n	Prominently effective	Improvement	Invalid	Effective rate
Sulodexide group	95	34	45	16	83.16 (79/95)
Jinshuibao group	90	25	44	21	76.67 (69/90)
Combined group	93	38	49	6	93.55 (87/93)*#

Notes: Compared with the sulodexide group, \* $P < 0.05$ ; Compared with the Jinshuibao group, # $P < 0.05$ .



**Figure 3.** The 24 h-UTP, UAER,  $\beta_2$ -MG, and Cys C levels. A. The 24 h-UTP levels in the three groups. B. The UAER levels in the three groups. C. The  $\beta_2$ -MG levels in the three groups. D. The Cys C levels in the three groups. Compared with before the treatment in the same group, \* $P < 0.05$ , \*\* $P < 0.01$ . Compared with after the treatment in the sulodexide group, # $P < 0.05$ . Compared with after the treatment in the Jinshuibao group,  $\Delta P < 0.05$ .

## Results

### Comparison of the clinical efficacy

The effective rate of the combined group (93.55%) was higher than the rate in the sulodexide group (83.16%) and the Jinshuibao group (76.67%) respectively, with statistically significant differences ( $P < 0.05$ ), as shown in **Table 1**.

### The 24 h-UTP, UAER, $\beta_2$ -MG, and Cys C levels

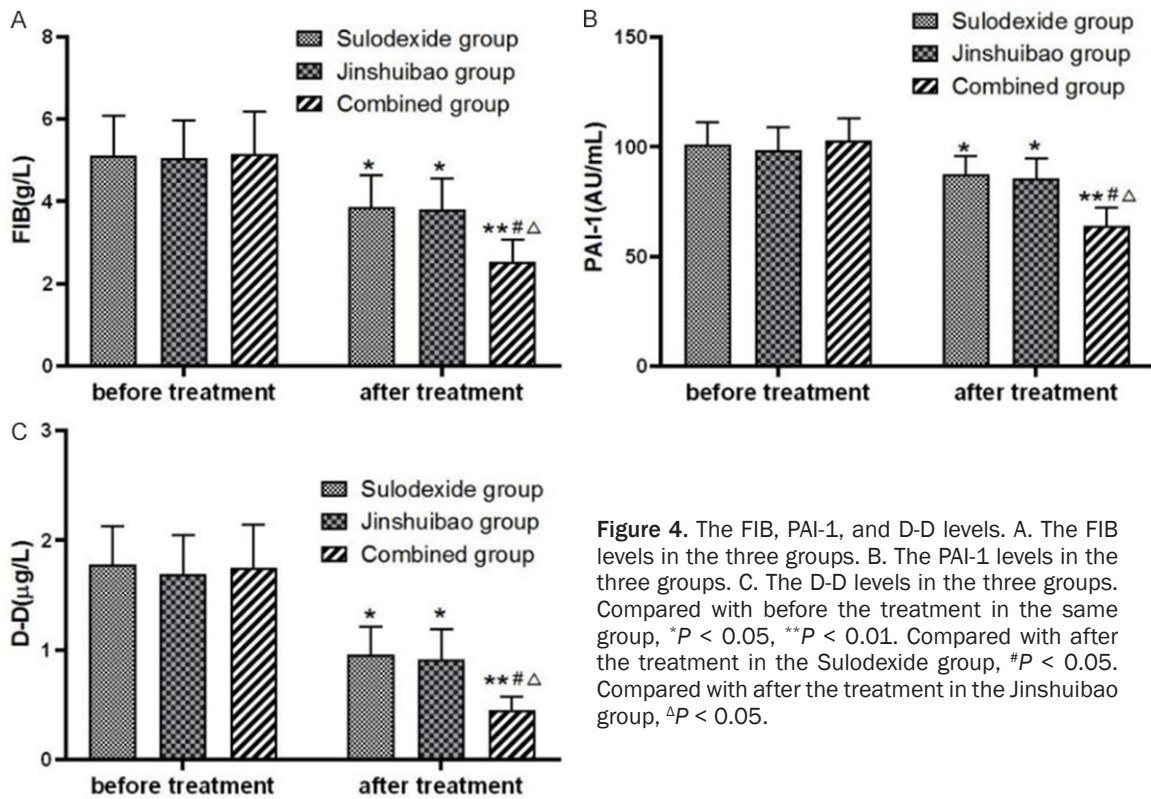
No significant difference were found in the 24 h-UTP, UAER,  $\beta_2$ -MG or Cys C levels in the three

groups before the treatment ( $P < 0.05$ ). After 8 weeks, the 24 h-UTP, UAER,  $\beta_2$ -MG, and Cys C levels in the three groups were significantly declined, and the 24 h-UTP, UAER,  $\beta_2$ -MG, and Cys C levels in the combined group were lower than they were in the sulodexide and Jinshuibao groups, with statistically significant differences ( $P < 0.05$ ), as shown in **Figure 3**.

### The FIB, PAI-1, and D-D levels

There were no significant differences in the FIB, PAI-1, or D-D levels in the three groups before the treatment ( $P > 0.05$ ). After the sulodexide, Jinshuibao, or combination treatment for 8

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**Figure 4.** The FIB, PAI-1, and D-D levels. A. The FIB levels in the three groups. B. The PAI-1 levels in the three groups. C. The D-D levels in the three groups. Compared with before the treatment in the same group, \* $P < 0.05$ , \*\* $P < 0.01$ . Compared with after the treatment in the Sulodexide group, # $P < 0.05$ . Compared with after the treatment in the Jinshuibao group,  $\Delta P < 0.05$ .

weeks, the FIB, PAI-1, and D-D levels were reduced considerably. What's more, the FIB, PAI-1, and D-D levels in the combined group were more alleviated than they were in the sulodexide group and the Jinshuibao group, with statistically significant differences ( $P < 0.05$ ), as shown in **Figure 4**.

### The ET-1, NO, and vWF levels

The sulodexide group, the Jinshuibao group, and the combination group didn't have significant differences in their ET-1, NO, and vWF levels before the treatment ( $P > 0.05$ ). After 8 weeks, the ET-1 and vWF levels in the three groups decreased notably, and the NO levels increased. In addition, the ET-1 and vWF levels in the combined group were much lower than they were in the sulodexide and Jinshuibao groups, and the NO levels were much higher, with statistically significant differences ( $P < 0.05$ ), as shown in **Figure 5**.

### The IL-6, TNF- $\alpha$ , and hs-CRP levels

There were no significant differences in the IL-6, TNF- $\alpha$ , or hs-CRP levels among the three groups before the treatment ( $P > 0.05$ ). After

the sulodexide, Jinshuibao, or combination treatment for 8 weeks, the IL-6, TNF- $\alpha$ , and hs-CRP levels in the three groups were reduced markedly, and the IL-6, TNF- $\alpha$ , and hs-CRP levels in the combined group were much lower than they were in the sulodexide and Jinshuibao groups, with statistically significant differences ( $P < 0.05$ ), as shown in **Figure 6**.

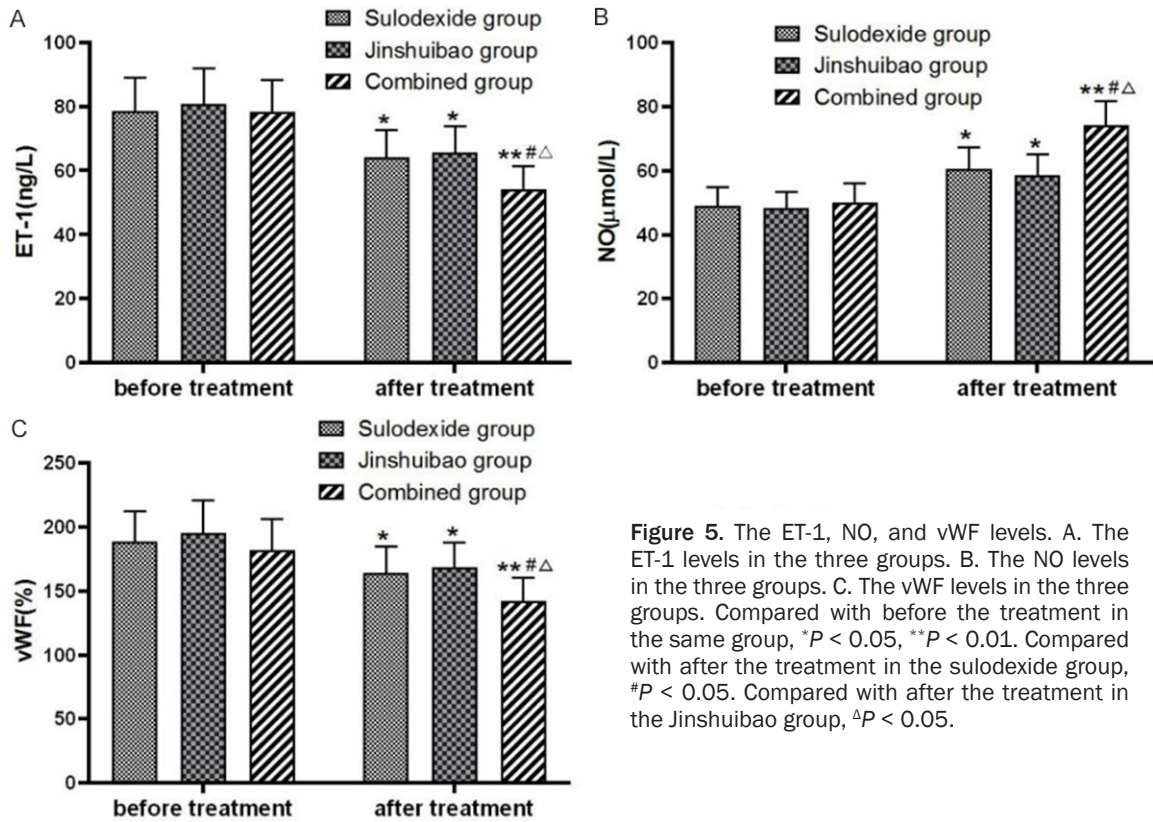
### The MDA and SOD levels

No significant differences were found in the MDA and SOD levels among the sulodexide, Jinshuibao, and combined groups before the treatment ( $P > 0.05$ ). After 8 weeks, the MDA levels in the three groups decreased notably, and the SOD levels were increased. In addition, the MDA levels in the combined group were much lower than they were in the sulodexide and Jinshuibao groups, but the SOD levels were much higher, with statistically significant differences ( $P < 0.05$ ). As shown in **Figure 7**.

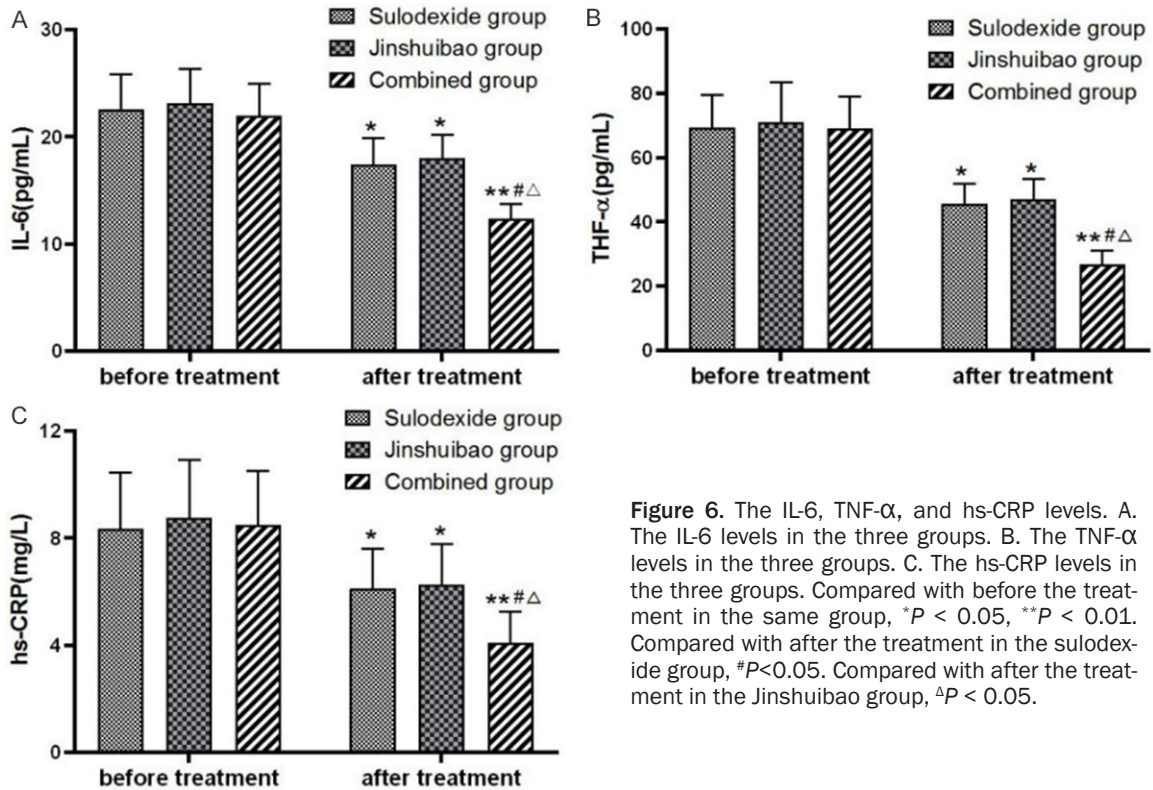
### Adverse reactions

During the treatment, 7 patients experienced mild nausea with abdominal distension in the sulodexide group, but without significant vomit-

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**Figure 5.** The ET-1, NO, and vWF levels. A. The ET-1 levels in the three groups. B. The NO levels in the three groups. C. The vWF levels in the three groups. Compared with before the treatment in the same group, \* $P < 0.05$ , \*\* $P < 0.01$ . Compared with after the treatment in the sulodexide group, # $P < 0.05$ . Compared with after the treatment in the Jinshuibao group, Δ $P < 0.05$ .

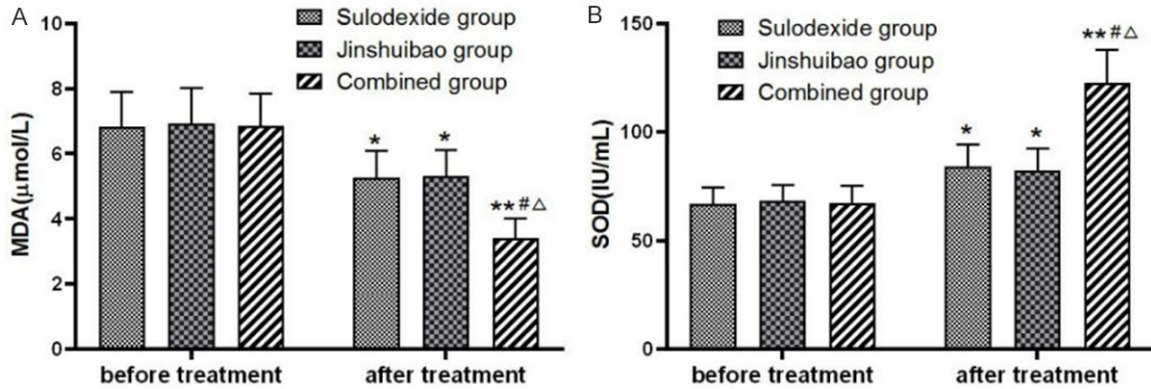


**Figure 6.** The IL-6, TNF-α, and hs-CRP levels. A. The IL-6 levels in the three groups. B. The TNF-α levels in the three groups. C. The hs-CRP levels in the three groups. Compared with before the treatment in the same group, \* $P < 0.05$ , \*\* $P < 0.01$ . Compared with after the treatment in the sulodexide group, # $P < 0.05$ . Compared with after the treatment in the Jinshuibao group, Δ $P < 0.05$ .

ing or abdominal pain. There were 6 cases of mild headache in the Jinshuibao group, 11

cases of mild nausea with abdominal distension, and 9 cases of mild headache in the com-

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**Figure 7.** The MDA and SOD levels. A. The MDA levels in the three groups. B. The SOD levels in the three groups. Compared with before the treatment in the same group, \* $P < 0.05$ , \*\* $P < 0.01$ . Compared with after the treatment in the sulodexide group, # $P < 0.05$ . Compared with after the treatment in the Jinshuibao group,  $\Delta P < 0.05$ .

combined group. None of the 3 groups had any other severe adverse reactions such as bleeding or abnormal liver function, etc.

### Discussion

DN is a common microvascular complications in DM, and its pathogenesis mainly includes microcirculation disturbances caused by abnormal glycolipid metabolism, the activation of the renin angiotensin aldosterone system (RAAS), the accumulation of glycosylation end products, inflammatory reactions, oxidative stress, and the activation of polyol pathways, etc. [12-14]. In addition, a hypercoagulable state and abnormal fibrinolysis also promote the occurrence and development of DN [15]. In the early stage of its pathophysiology, the proliferation of glomerular mesangial cells, the thickening of the basement membrane, and glomerulosclerosis are the main manifestations. With the progress of the disease, podocytes, the renal interstitium, renal tubular and renal arterioles lesions can gradually appear [16, 17].

Microalbuminuria is a clinical marker of early DN, if not well controlled, large amounts of albuminuria may occur. Albuminuria can predict a decrease in the glomerular filtration rate (GFR), an important indicator of DN. Therefore, controlling the formation of albuminuria and shortening the course of albuminuria are keys to delaying the progress of DN and even reversing DN. Currently, the clinical indicators used to reflect albuminuria mainly include 24 h-UTP, UAER, and  $\beta_2$ -MG, etc. [18]. Among them,  $\beta_2$ -MG is a small molecular protein, almost all of which

are filtered by glomeruli. Normally, about 99.9% are reabsorbed by the proximal convoluted tubule epithelial cells, and when renal tubulars are damaged, especially proximal convoluted tubular injuries, the reabsorption function decreases, and the urinary  $\beta_2$ -MG level can increase significantly.  $\beta_2$ -MG is a marker of renal tubular injury, and it plays an important role in the early diagnosis of DN [19]. Cys C belongs to the family of serum cysteinease inhibitors, which can pass through glomerular filtration membranes freely, and is almost completely reabsorbed by renal tubulars and not interfered by blood glucose, lipids, inflammation, or other factors. Cys C has a higher sensitivity and specificity compared with creatinine, and it is a more ideal index to reflect GFR, and it is currently widely used in the diagnosis and differential diagnosis of early DN [20, 21]. In recent years, researchers have found that the hypercoagulable state and abnormal fibrinolysis play important roles in the occurrence and development of DN. FIB is the precursor of thrombus, which reflects hypercoagulability and fibrinolytic activity. Its elevation can increase the viscosity of whole blood and form glomerular microthrombus [22]. Increasing levels of PAI-1 may lead to weakened local fibrinolysis and can induce thrombus [23]. D-D is a specific degradation product of fibrin monomers through fibrinolytic hydrolysis, and it is a fibrinolytic marker and reflects the function of fibrinolysis [24]. In our study, we found that the combined treatment of sulodexide and Jinshuibao in DN patients at the early stage can reduce the levels of 24 h-UTP, UAER,  $\beta_2$ -MG, Cys C, FIB, PAI-1 and D-D, which indicates that the combination

of these two drugs can improve renal function and reduce the hyperfunction of coagulation systems for early DN.

Vascular endothelial function changes with the development of DN. Vascular epithelial cells are a layer of monocytes located between the vascular wall and the blood flow, and they can secrete active substances such as ET-1, NO, and vWF to stimulate renal vasoconstriction, reduce renal blood perfusion, promote vascular smooth muscle hyperplasia, and increase collagens, which are a key inducement of proteinuria [25, 26]. IL-6 can promote the proliferation of mesangial cells, glomerulosclerosis, capillary permeability, the secretion of inflammatory factors, and can aggravate the renal injury [27]. High levels of TNF- $\alpha$  and hs-CRP can impair the microvessels and vascular endothelial cells, and can result in the thickening and reduced elasticity of vascular walls, as well as proteinuria, thus promoting the occurrence and development of DN [28]. SOD and MDA are sensitive indices reflecting oxidative stress levels. SOD can effectively remove superoxide anions and regulate the balance of oxidant and antioxidant reactions, and it can represent the ability of scavenging reactive oxygen free radicals of the organism [29]. MDA belongs to the family of peroxide products of unsaturated fatty acids and is a direct indicator of vascular injury [30]. Sulodexide is a glycosaminoglycan drug, and its protective mechanism for DN may include promoting renal microcirculation, protecting glomerular filtration membranes, inhibiting mesangial stromal cell proliferation, anti-inflammatory reactions and oxidative stress, etc. [31, 32]. Liu's [33] research showed that sulodexide protects renal tubular epithelial cells from oxidative stress-induced injuries by upregulating the expression of the KLOTHO gene at an early stage of DN. Jinshuibao is a fermented CS-4 strain of *Cordyceps sinensis*, which contains varieties of amino acids, trace elements, and vitamins. It can improve renal microcirculation, inhibit platelet accumulation, renal tubular atrophy, and interstitial fibrosis, reduce albuminuria excretion, and improve renal function [34]. Our research indicates that the combined treatment of sulodexide and Jinshuibao in DN patients at the early stage can decrease ET-1, vWF, IL-6, TNF- $\alpha$ , hs-CRP, and MDA levels, and increase NO and SOD levels, showing that the combination of sulodexide and Jinshuibao has certain therapeutic effects on early DN.

### Conclusion

This study explored the effect of the combined treatment of sulodexide and Jinshuibao on early DN, and our results suggest that the combination of these two drugs can reduce the formation of albuminuria, decrease the hyperfunction of the coagulation system, promote the anti-inflammatory effect, and improve vascular epithelial function and the oxidative stress reaction. The combined treatment decelerates DN progression and protects against renal injury, and it is an effective treatment for early DN and has further value in clinical applications. Nevertheless, there are some weaknesses in this study, such as the small sample size, which may affect the results. The specific mechanism of the protective effect of sulodexide and Jinshuibao on renal protection in early DN has not been further clarified, so it needs further multi-center based, in-depth research in the future.

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### Disclosure of conflict of interest

None.

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