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Original Article

Effect of alprostadil combined with sulodexide on elderly chronic kidney disease patients and the independent risk factors affecting curative results

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Abstract: Objectives: Chronic kidney disease (CKD) is a global public health concern with high prevalence in the elderly. The study was designed to investigate curative efficacy of alprostadil in conjunction with sulodexide on elderly CKD patients and identify risk factors affecting treatment outcomes. Methods: This retrospective study enrolled 257 elderly CKD patients treated in our hospital from September 2020 to September 2024. Patients were divided into the alprostadil group (n = 122) and the alprostadil + sulodexide group (n = 135) based on treatment regimen. Serum creatinine (Scr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), and 24-hour urinary protein (24 h-UTP) were measured before and after 4 weeks of treatment. Therapeutic efficacy and adverse events were evaluated. Results: After treatment, the combination group showed significantly lower Scr (P = 0.001), higher eGFR (P = 0.007), and reduced UACR (P < 0.001) and 24 h-UTP (P < 0.001) compared to the alprostadil group. The total effective rate was significantly higher in the combination group (P = 0.009). Multivariate analysis identified age, diabetes, baseline Scr, and baseline UACR as independent risk factors for poor efficacy, while combination therapy was a protective factor. Receiver operating characteristic (ROC) analysis showed that Scr [area under the curve (AUC) = 0.712] and UACR (AUC = 0.722) had moderate predictive value for treatment efficacy. Conclusion: Alprostadil combined with sulodexide significantly improves renal function and clinical efficacy in elderly patients with CKD, and baseline Scr and UACR serve as useful predictors of treatment response.

Keywords: Renal insufficiency, chronic, alprostadil, drug therapy, combination, risk factors, aged, treatment outcome

Introduction

Emerging as a significant non-communicable health issue on a global scale, chronic kidney disease (CKD) now poses a considerable challenge to public health systems around the world. Findings from the Global Burden of Disease 2023 report indicate that approximately 788 million adults were living with CKD, nearly doubling the cases reported in 1990 [1]. This progressive condition now ranks as the ninth leading cause of death globally, accounting for 1.48 million deaths annually [2]. The rising prevalence is particularly pronounced in older populations, with data indicating that approximately 34% of individuals aged 65 years and older have CKD, compared to only 6% of adults aged 18-44 years [3].

The burden of CKD extends beyond its direct impact on renal function. The disease is inextricably tied to cardiovascular morbidity and mortality, a relationship formalized in the concept of cardiovascular-kidney-metabolic syndrome [4]. Even mild reductions in estimated glomerular filtration rate are linked to a 1.4- to 2-fold elevated risk of cardiovascular events, with studies showing that individuals with CKD have a four-fold higher estimated 10-year cardiovascular risk than those without the condition [5]. The pathophysiological mechanisms underlying this heightened risk include chronic inflammation, oxidative stress, accumulation of uremic toxins, and disturbances in mineral metabolism, all of which begin to manifest in early-stage disease [6].

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Among the various populations affected by CKD, elderly patients warrant particular attention due to their unique clinical characteristics. Age-related physiological changes, including reduced renal reserve and altered drug metabolism, complicate disease management [7]. Furthermore, elderly patients frequently present with multiple comorbidities - particularly hypertension, diabetes, and cardiovascular disease - that both contribute to CKD progression and complicate treatment strategies [8]. These interconnected conditions create a complex clinical scenario requiring careful therapeutic optimization [9].

The therapeutic landscape for CKD has evolved considerably, yet significant challenges remain. Alprostadil, a prostaglandin E1 analog, has demonstrated renoprotective properties through multiple mechanisms. By increasing cyclic adenosine monophosphate concentrations, dilating renal vessels, increasing renal blood flow, and inhibiting renin-angiotensin-aldosterone system, alprostadil improves renal hemodynamics, and microcirculation [10]. Experimental studies indicate that alprostadil treatment significantly reduces renal damage parameters in diabetic nephropathy models, effects mediated in part through down-regulation of angiopoietin-2 and interleukin-18 expression in glomerular endothelial cells [11].

Sulodexide, a highly purified mixture of glycosaminoglycans composed of 80% fast-moving heparin fraction and 20% dermatan sulfate, offers a complementary mechanism of action [12]. This agent concentrates in renal parenchyma and acts as an effective inhibitor of heparanase-1, preventing degradation of heparan sulfate in the glomerular basement membrane and thus restoring ionic permselectivity [13]. Clinical evidence suggests sulodexide reduces albuminuria in diabetic nephropathy patients, with a meta-analysis confirming its renal protective effects [14]. The antiproteinuric effect appears to be mainly related to basal proteinuria levels and duration of treatment.

Given the distinct yet complementary mechanisms of these two agents - alprostadil targeting hemodynamic factors and sulodexide addressing structural integrity of the glomerular filtration barrier - their combination may offer synergistic benefits in elderly CKD patients. However, clinical evidence supporting combination therapy in this specific population remains limited. Furthermore, identifying factors that predict therapeutic response could enable more personalized treatment approaches. The present study therefore aimed to investigate the curative effect of alprostadil combined with sulodexide in elderly patients (aged ≥ 60 years) with CKD, and to identify independent risk factors affecting treatment outcomes.

Data and methods

Clinical data of patients

This study enrolled 257 elderly patients with chronic kidney disease (CKD) who were treated in Tianjin Fourth Central Hospital from September 2020 to September 2024. Based on the treatment regimen, patients were divided into two groups: the alprostadil group (n = 122) received alprostadil alone, and the alprostadil + sulodexide group (n = 135) received alprostadil combined with sulodexide. The research protocol received review and approval from the Medical Ethics Committee at Tianjin Fourth Central Hospital. As this study entailed a retrospective analysis of de-identified patient data obtained during routine clinical practice, and no additional interventions or patient contacts were involved, the Ethics Committee granted a waiver of informed consent. All procedures were performed in compliance with applicable privacy regulations.

Screening criteria

Inclusion criteria: The patient was diagnosed with CKD and received treatment in our hospital. The clinical data were complete. The patient was aged ≥ 60 years old and had a primary school education or above. The patients could cooperate with the investigation.

Exclusion criteria: Patients who died in the course of treatment; patients combined with other tumors; patients with physical disability; patients transferred to other hospital; patients resistant or allergic to the drugs used in this study; patients accompanied with mental diseases and language dysfunction; patients who had diseases affecting the results of this study.

Although this was a retrospective study, sample size was calculated according to total number of patients who fulfilled the inclusion crite-

ria between September 2020 and September 2024. No a priori power calculation was performed; instead, all consecutive patients meeting the criteria were enrolled to minimize selection bias and ensure representativeness.

Treatment plan for patients

The alprostadil group was treated with alprostadil alone (Harbin pharmaceutical group bioengineering Co., Ltd., SFDA Approval No. H20059787), with 1-2 ml + 10 ml normal saline (or 5% glucose) intravenously, once a day. The alprostadil + sulodexide group was treated with alprostadil combined with sulodexide, and the medication delivery of alprostadil was the same as that of the control group. Sulodexide (Italian Alfa Wassermann Pharmaceutical Company, Registration standard for imported drugs JX20030143) was used with 250 LSU orally, twice a day. The dosage was adjusted according to the patient's physical condition. Both groups were given drugs continuously for 4 weeks, and statistical analysis was carried out after 4 weeks. During treatment, the physical condition of patients was closely monitored, and timely symptomatic treatment was carried out in case of abnormal conditions.

Evaluation of clinical efficacy of patients

Evaluation criteria of therapeutic effect: markedly effective: clinical symptoms of patients were relieved, signs disappeared, and Serum creatinine (Scr) level decreased by more than (or equal to) 50%. Effective: the clinical symptoms of the patient were improved and the Scr level was reduced to 20%-50%. Ineffective: the clinical symptoms and signs of the patient did not improve.

Laboratory measurements

Venous blood samples (5 mL) were drawn from each participant after an overnight fast, one day prior to the initiation of treatment and again at the conclusion of the 4-week treatment period. Blood samples were permitted to rest for 30 minutes before being centrifuged at 3,000 rpm for 10 minutes. The supernatant was harvested for further analysis. Serum creatinine (Scr) and urinary albumin were measured using double antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA). The Scr ELISA kit was purchased from Shanghai Hengdu Biotechnology Co., Ltd. (item number: HD39799), and the albuminuria kit was purchased from Shanghai Bluegene Biotech Co., Ltd. (item number: E01U0011). Blood urea nitrogen (BUN) was measured using an automated biochemical analyzer (Hitachi 7600, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. The first morning urine sample was collected; the initial stream was discarded, and the mid-stream urine was used for measurement of urinary albumin and creatinine. Urinary albumin-to-creatinine ratio (UACR) was determined by dividing urinary albumin concentration (mg) by urinary creatinine concentration (g). Urinary creatinine was measured using the same automated biochemical analyzer. The 24-hour urinary protein (24 h-UTP) was measured by turbidimetric method using a commercial kit (Nanjing Jiancheng Bioengineering Institute, China). All procedures were performed according to the manufacturers' instructions.

Observation indicators

Main indicators: the enhancement in clinical efficacy among the two patient groups following treatment and the risk factors influencing the treatment outcomes for elderly CKD patients.

Secondary indicators: the level of renal function indicators (Scr, BUN, eGFR) and urinary protein indicators (UACR, 24 h-UTP), adverse events, predictive value of Scr and UACR for therapeutic effect.

Statistical methods

Data were analyzed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Continuous variables that followed a normal distribution were reported as means ± standard deviations and compared using independent-sample t-tests between groups. Categorical variables were presented as frequencies and percentages, with comparisons made using chi-square tests. To determine the independent risk factors affecting efficacy, both univariate and multivariate logistic regression analyses were conducted. Receiver operating characteristic (ROC) curve analysis was conducted to assess the predictive value of Scr and UACR for efficacy. A P-value < 0.05 was considered statistically significant. All tests were two-sided.

Table 1. Baseline demographic patient data

Parameters	Alprostadil group (n = 122)	Alprostadil + sulodexide group (n = 135)	t/χ^2	P
Age (years)	71.85 ± 2.82	72.21 ± 3.01	0.991	0.323
Sex [n (%)]			0.112	0.738
Male	73 (59.84)	78 (57.78)		
Female	49 (40.16)	57 (42.22)		
BMI (kg/m^2)	22.21 ± 2.15	22.35 ± 2.27	0.509	0.611
Marital situation [n (%)]			0.527	0.468
Married	113 (92.62)	128 (94.81)		
Unmarried	9 (7.38)	7 (5.19)		
Nationality [n (%)]			0.924	0.336
Han	79 (64.75)	95 (70.37)		
Minorities	43 (35.25)	40 (29.63)		
Residence [n (%)]			0.065	0.799
Urban	67 (54.92)	72 (53.33)		
Rural	55 (45.08)	63 (46.67)		
Smoking [n (%)]			0.820	0.365
Yes	79 (64.75)	80 (59.26)		
No	43 (35.25)	55 (40.74)		
Drinking [n (%)]			0.171	0.679
Yes	70 (57.38)	74 (54.81)		
No	52 (42.62)	61 (45.19)		
Exercise [n (%)]			0.698	0.403
Yes	40 (32.79)	51 (37.78)		
No	82 (67.21)	84 (62.22)		

BMI: body mass index.

Results

Baseline condition

A total of 257 elderly patients with CKD were included in this retrospective study, with 122 patients in alprostadil group and 135 patients in alprostadil + sulodexide group. **Table 1** indicates no notable variations between the two groups regarding age, sex, body mass index (BMI), marital status, nationality, residence, smoking, drinking, or exercise habits (all P > 0.05), indicating that the two groups were well-balanced and comparable at baseline (**Table 1**).

Table 2 presents baseline clinical features of patients. The distribution of CKD stages (Stage 3 vs. Stage 4) was similar between two groups (P = 0.661). Prevalence of comorbidities such as hypertension, diabetes, coronary heart disease, and cerebrovascular disease did not differ notably between the groups (all P > 0.05), further confirming the comparability of the cohorts (**Table 2**).

Renal function indicators

The changes in renal function indicators before and after treatment are summarized (**Figure 1**). Prior to treatment, there were no significant differences between the two groups in Scr, BUN, or eGFR (all P > 0.05). After four weeks of treatment, the alprostadil + sulodexide group demonstrated significantly greater reductions in Scr compared to the alprostadil group (196.43 ± 52.18 μmol/L vs. 218.54 ± 55.31 μmol/L, P = 0.001). Similarly, the post-treatment eGFR was significantly higher in the alprostadil + sulodexide group than in the alprostadil group (49.33 ± 14.57 mL/min/1.73 m^2 vs. 44.56 ± 13.24 mL/min/1.73 m^2, P = 0.007). Difference of BUN levels between groups post-treatment didn't reach statistical significance (P = 0.107).

Urinary protein index

Figure 2 displays the changes in urinary protein indices. At baseline, no notable variations were observed between two groups concerning UACR or 24 h-UTP (both P > 0.05). Following

Table 2. Baseline clinical features between the two groups [n (%)]

Parameters	Alprostadil group (n = 122)	Alprostadil + sulodexide group (n = 135)	χ^2	P
CKD stage			0.192	0.661
Stage 3	80 (65.57)	92 (68.15)		
Stage 4	42 (34.43)	43 (31.85)		
Comorbidity				
Hypertension	102 (83.61)	115 (85.19)	0.122	0.727
Diabetes	76 (62.30)	88 (65.19)	0.232	0.630
Coronary heart disease	47 (38.52)	55 (40.74)	0.131	0.717
Cerebrovascular disease	33 (27.05)	36 (26.67)	0.005	0.945

CKD: chronic kidney disease.

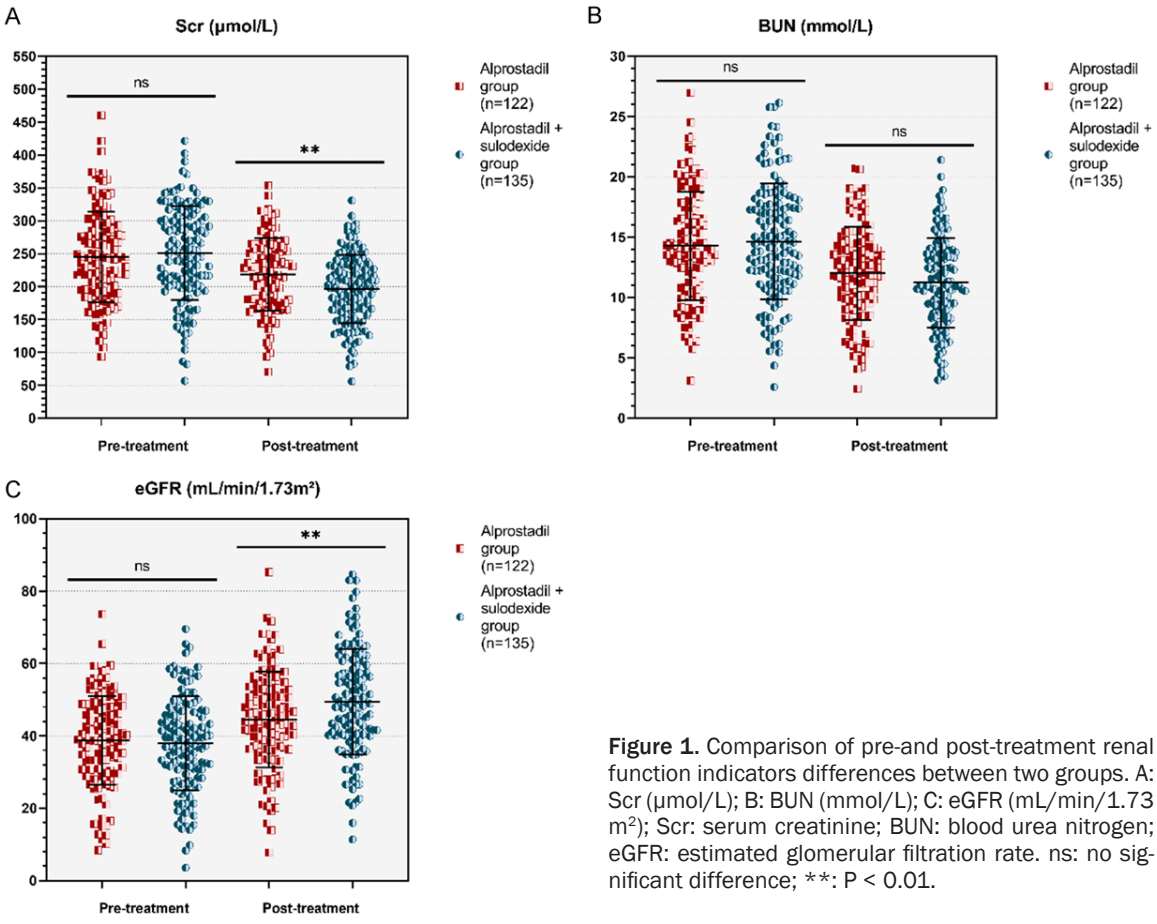

Figure 1. Comparison of pre-and post-treatment renal function indicators differences between two groups. A: Scr (μmol/L); B: BUN (mmol/L); C: eGFR (mL/min/1.73 m^2); Scr: serum creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate. ns: no significant difference; **: P < 0.01.

treatment, the alprostadil + sulodexide group exhibited significantly lower UACR (542.67 ± 162.38 mg/g vs. 654.23 ± 185.42 mg/g, P < 0.001) and 24 h-UTP (1.24 ± 0.53 g/24 h vs. 1.52 ± 0.61 g/24 h, P < 0.001) than the alprostadil group. These results indicate that addition of sulodexide to alprostadil therapy provides a superior reduction in proteinuria (**Figure 2**).

Therapeutic efficacy of patients

The clinical efficacy of the two treatment regimens is compared in **Table 3**. The overall effective treatment rate was significantly higher in the alprostadil + sulodexide group compared to the alprostadil group (81.48% vs. 67.21%, P = 0.009). Notably, the percentage of patients achieving a "markedly effective" outcome was

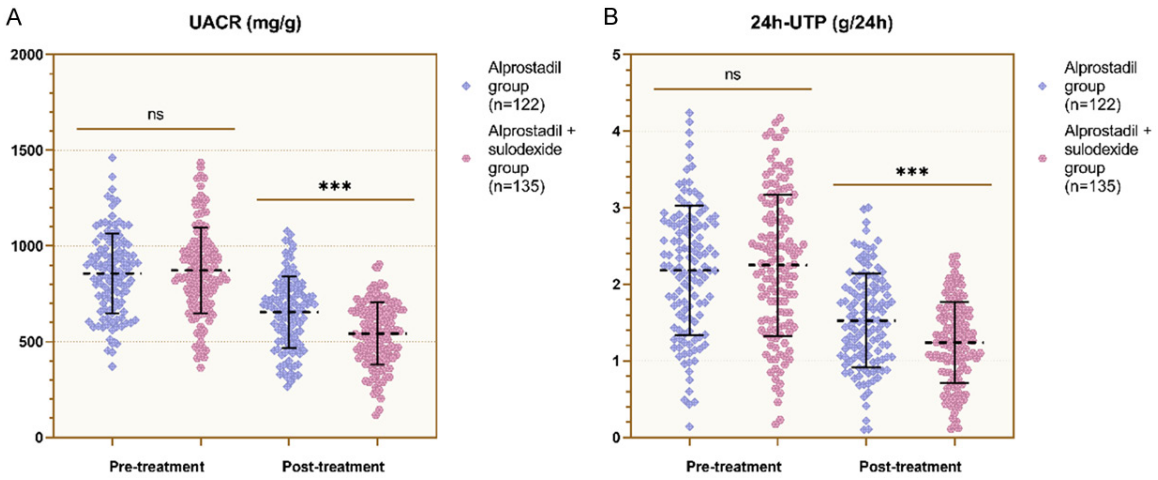

Figure 2. Comparison of pre-and post-treatment urinary protein index between two groups. A: UACR (mg/g); B: 24 h-UTP (g/24 h); UACR: urinary albumin-to-creatinine ratio; 24 h-UTP: 24-hour urinary protein. ns: no significant difference; ***: P < 0.001.

Table 3. Comparison of therapeutic efficacy of patients between the two groups [n (%)]

Parameters	Alprostadil group (n = 122)	Alprostadil + sulodexide group (n = 135)	χ^2	P
Total effective treatment rate (Markedly effective + Effective)	82 (67.21)	110 (81.48)	6.905	0.009
Markedly effective	32 (26.23)	58 (43.96)		
Effective	50 (41.98)	52 (38.52)		
Ineffective	40 (32.79)	25 (18.52)		

Table 4. Comparison of adverse events between the two groups [n (%)]

Parameters	Alprostadil group (n = 122)	Alprostadil + sulodexide group (n = 135)	χ^2	P
Total adverse events	37 (30.33)	51 (37.78)	1.580	0.209
Injection site reactions (redness, pain)	9 (7.38)	11 (8.15)		
Facial flushing/palpitations	15 (12.30)	19 (14.07)		
Headache/dizziness	7 (5.74)	9 (6.67)		
Gastrointestinal discomfort	5 (4.10)	8 (5.93)		
Bleeding tendency (ecchymosis, etc.)	1 (0.82)	4 (2.96)		

substantially greater in the alprostadil + sulodexide group (43.96% vs. 26.23%), while the rate of ineffective treatment was lower (18.52% vs. 32.79%). These findings suggest that the combination of alprostadil and sulodexide offers a significant therapeutic advantage over alprostadil alone (**Table 3**).

Safety evaluation

Table 4 summarizes the adverse events observed during the study period. The overall incidence of adverse events was slightly higher in the alprostadil + sulodexide group (37.78%) compared to the alprostadil group (30.33%), but this difference was not statistically significant (P = 0.209). The most frequently reported adverse events included injection site reactions, facial flushing or palpitations, headache or dizziness, and gastrointestinal discomfort. Notably, there was a slight increase in bleeding tendency (ecchymosis, etc.) in the alprostadil + sulodexide group (2.96% vs. 0.82%), although this did not reach statistical significance.

Table 5. Univariate analysis of baseline characteristics between effective and ineffective groups of patients

Parameters	Effective group (n = 192)	Ineffective group (n = 65)	t/χ^2	P
Age (years)	71.28 ± 2.96	74.31 ± 3.22	6.970	< 0.001
Male [n (%)]	108 (56.26)	39 (60.00)	0.279	0.597
BMI (kg/m^2)	22.31 ± 2.18	22.42 ± 2.31	0.328	0.743
Smoking [n (%)]	62 (32.29)	28 (43.08)	2.482	0.115
Drinking [n (%)]	46 (24.96)	19 (29.23)	0.714	0.398
Exercise [n (%)]	66 (34.38)	24 (36.92)	0.139	0.710
Combination therapy [n (%)]	110 (57.29)	25 (38.46)	6.905	0.009
CKD stage (Stage 3/Stage 4) [n (%)]	133 (69.27)	38 (58.46)	2.548	0.110
Hypertension [n (%)]	152 (79.17)	58 (89.23)	3.291	0.070
Diabetes mellitus [n (%)]	112 (58.33)	52 (80.00)	9.872	0.002
Coronary heart disease [n (%)]	74 (38.55)	28 (43.08)	0.417	0.518
Cerebrovascular disease [n (%)]	45 (23.45)	18 (27.69)	0.475	0.491
Baseline Scr (μmol/L)	236.47 ± 64.28	281.35 ± 75.49	5.858	< 0.001
Baseline BUN (mmol/L)	14.12 ± 4.43	15.31 ± 5.12	1.798	0.073
Baseline eGFR (mL/min)	39.74 ± 12.58	34.89 ± 13.11	2.656	0.008
Baseline UACR (mg/g)	832.14 ± 201.47	961.28 ± 241.36	5.699	< 0.001
Baseline 24 h-UTP (g/24 h)	2.15 ± 0.84	2.42 ± 0.98	2.149	0.033

BMI: body mass index; CKD: chronic kidney disease; Scr: serum creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; 24 h-UTP: 24-hour urinary protein.

Importantly, all adverse events were mild to moderate in severity and did not lead to treatment discontinuation (**Table 4**).

Analysis of risk factors affecting therapeutic efficacy

Univariate analysis of baseline characteristics between effective and ineffective groups of patients: To identify factors associated with treatment outcome, patients were stratified into an effective group (n = 192) and an ineffective group (n = 65) based on their response to therapy. **Table 5** presents the univariate analysis comparing baseline characteristics between these two groups. Patients in the ineffective group were significantly older (74.31 ± 3.22 years vs. 71.28 ± 2.96 years, P < 0.001) and had a higher prevalence of diabetes (80.00% vs. 58.33%, P = 0.002). The proportion of patients receiving combination therapy was significantly lower in the ineffective group (38.46% vs. 57.29%, P = 0.009). Furthermore, patients with poor treatment response had significantly higher baseline levels of Scr (281.35 ± 75.49 μmol/L vs. 236.47 ± 64.28 μmol/L, P < 0.001), UACR (961.28 ± 241.36 mg/g vs. 832.14 ± 201.47 mg/g, P < 0.001), and 24 h-UTP (2.42 ± 0.98 g/24 h vs. 2.15 ± 0.84 g/24 h, P = 0.033), as well as lower baseline eGFR (34.89 ± 13.11 mL/min vs. 39.74 ± 12.58 mL/min, P = 0.008). No notable variations were found between the two groups in terms of sex, BMI, smoking, drinking, exercise, CKD stage, hypertension, coronary heart disease, cerebrovascular disease, or baseline BUN (**Table 5**).

Multivariate logistic regression analysis of independent risk factors affecting efficacy: **Table 6** displays the results of multivariate logistic regression analysis, which was performed to identify independent risk factors for poor therapeutic efficacy. After adjusting for potential confounders, age (OR = 1.441, 95% CI: 1.256-1.654, P < 0.001), diabetes mellitus (OR = 2.820, 95% CI: 1.193-6.668, P = 0.018), baseline Scr (OR = 1.016, 95% CI: 1.010-1.023, P < 0.001), and baseline UACR (OR = 1.005, 95% CI: 1.003-1.007, P < 0.001) emerged as significant independent risk factors for treatment failure. Conversely, combination therapy was identified as an independent protective factor against poor efficacy (OR = 0.321, 95% CI: 0.145-0.712, P = 0.005) (**Table 6**).

Predictive value of Scr and UACR for efficacy: Baseline Scr and UACR were assessed for their predictive value regarding treatment efficacy

Table 6. Multivariate logistic regression analysis of independent risk factors affecting efficacy

Parameters	Coefficient	Std_Error	Wald χ^2	P	OR (95% CI)
Age	0.366	0.070	5.212	< 0.001	1.441 (1.256-1.654)
Combination therapy	-1.135	0.406	-2.795	0.005	0.321 (0.145-0.712)
Diabetes mellitus	1.037	0.439	2.362	0.018	2.820 (1.193-6.668)
Baseline Scr	0.016	0.003	4.852	< 0.001	1.016 (1.010-1.023)
Baseline UACR	0.005	0.001	4.423	< 0.001	1.005 (1.003-1.007)

OR: odds ratio; CI: confidence interval; Scr: serum creatinine; UACR: urinary albumin-to-creatinine ratio. Dependent variable: efficacy (0 = effective, 1 = ineffective).

Table 7. Predictive value of Scr and UACR for efficacy

Parameters	Best_threshold	Sensitivities	Specificities	AUC	Youden_index
Scr (μmol/L)	256.73	0.692	0.688	0.712	0.380
UACR (mg/g)	907.75	0.708	0.719	0.722	0.427

AUC: area under the curve; Scr: serum creatinine; UACR: urinary albumin-to-creatinine ratio.

through ROC curve analysis. For Scr, optimal threshold for predicting treatment efficacy was 256.73 μmol/L, yielding an area under the curve (AUC) of 0.712 (sensitivity: 69.20%, specificity: 68.80%). For UACR, optimal threshold was 907.75 mg/g, with an AUC of 0.722 (sensitivity: 70.80%, specificity: 71.90%). These findings suggest that both Scr and UACR have moderate predictive value for identifying patients who are less likely to respond favorably to treatment (**Table 7**).

Discussion

The present study demonstrates that combination therapy with alprostadil and sulodexide confers therapeutic advantages over alprostadil monotherapy in elderly patients with CKD. Patients receiving combination therapy exhibited greater improvements in renal function parameters, including reduced Scr and increased estimated glomerular filtration rate, alongside more pronounced reductions in proteinuria as measured by urinary albumin-to-creatinine ratio and 24-hour urinary protein excretion. These physiological improvements translated into higher treatment efficacy rates, with a substantially greater proportion of combination therapy patients achieving marked clinical responses.

The complementary mechanisms of action of these two agents likely underlie the observed synergistic effects. Alprostadil, as a prostaglandin E1 analog, primarily targets hemodynamic pathways by inducing renal vasodilation, increasing renal blood flow, and inhibiting the renin-angiotensin-aldosterone system [15, 16]. These effects improve renal microcirculation and may enhance delivery of sulodexide to target tissues. Sulodexide, conversely, acts on structural components of the glomerular filtration barrier. By inhibiting heparanase-1, it prevents degradation of heparan sulfate in the glomerular basement membrane, thereby restoring ionic permselectivity and reducing protein leakage [17]. Experimental studies have confirmed that sulodexide administration reduces albuminuria in diabetic nephropathy models through preservation of glomerular basement membrane integrity [18, 19]. The convergence of hemodynamic optimization and structural repair mechanisms provides a rational basis for the enhanced efficacy observed with combination therapy. Furthermore, growing evidence suggests that certain renoprotective agents may act in part by inducing heat shock proteins (HSPs), which exert anti-inflammatory and anti-apoptotic effects in renal tissue during injury. For instance, glutamine has been shown to attenuate renal ischaemia-reperfusion injury through upregulation of HSP expression [20]. Although the direct HSP-inducing effect of alprostadil or sulodexide requires further investigation, the observed reduction in renal injury in our study may involve similar endogenous protective pathways.

The superior reduction in proteinuria observed with combination therapy carries particular clinical significance. Proteinuria functions not

merely as a marker of kidney damage but as an active mediator of disease progression, promoting tubular injury, interstitial inflammation, and fibrotic pathways that accelerate renal decline [21]. Sulodexide's ability to restore glomerular basement membrane integrity addresses the structural determinants of protein leakage that hemodynamic agents alone cannot fully correct. Previous investigations have documented sulodexide's antiproteinuric effects across various CKD etiologies, including diabetic nephropathy, hypertensive nephropathy, and primary glomerulonephritis [22, 23]. The current findings extend these observations by demonstrating additive benefits when sulodexide is combined with a vasoactive agent in an elderly population.

The safety profile of combination therapy warrants consideration. Although the combination group exhibited a numerically higher overall incidence of adverse events, this difference did not achieve statistical significance. The observed events - including injection site reactions, facial flushing, headache, and gastrointestinal discomfort - were consistent with the known safety profiles of both medications and were generally mild to moderate in severity. The slight increase in bleeding tendency, while not statistically different, merits attention given the anticoagulant properties of sulodexide's heparin component [24]. However, the absence of treatment discontinuations suggests acceptable tolerability in this elderly population [25].

Multivariate analysis identified several independent predictors of poor therapeutic response. Advanced age emerged as a risk factor for treatment failure, reflecting the complex interplay between physiological aging and disease progression [26]. Elderly patients possess reduced renal reserve, altered drug metabolism, and diminished capacity for tissue repair, all of which may attenuate therapeutic responses [27]. Age-related nephron loss and impaired regenerative capacity limit the kidney's ability to recover functionally even when hemodynamic and structural insults are addressed [28]. These findings underscore the need for early intervention before age-related renal changes become established.

Diabetes mellitus similarly predicted poorer outcomes, consistent with its established role in accelerating CKD progression [29]. Diabetic nephropathy involves multiple pathogenic mechanisms beyond those targeted by either alprostadil or sulodexide, including advanced glycation end-product accumulation, oxidative stress, and pro-inflammatory cytokine activation [30, 31]. The persistent hyperglycemic milieu may create irreversible structural damage - such as glomerular basement membrane thickening, mesangial expansion, and nodular glomerulosclerosis - that limits responsiveness to interventions primarily targeting hemodynamic and permselectivity pathways [32]. These observations suggest that diabetic patients may require more intensive monitoring and earlier treatment initiation.

Baseline Scr and urinary albumin-to-creatinine ratio emerged as powerful predictors of therapeutic efficacy, with higher values associated with increased likelihood of treatment failure. This relationship reflects the extent of established renal damage at treatment initiation - patients presenting with more advanced disease have less functional reserve to recover and may have already developed irreversible fibrotic changes [33]. Proteinuria, in particular, indicates not only glomerular barrier dysfunction but also ongoing tubular injury and interstitial inflammation that may be less amenable to reversal. The moderate predictive value of these biomarkers suggests they can usefully inform clinical decision-making. Patients exceeding the identified thresholds may require more intensive monitoring, alternative treatment strategies, or earlier consideration of combination therapy [34, 35].

Importantly, combination therapy itself emerged as an independent protective factor against poor efficacy, with an odds ratio substantially below unity. This finding persisted after adjustment for potential confounders, reinforcing the conclusion that the observed benefits are derived from the therapeutic intervention rather than baseline differences between groups. The protective effect of combination therapy likely stems from its dual targeting of both hemodynamic and structural determinants of CKD progression, addressing the multifactorial nature of renal decline in elderly patients.

The key novel findings of this study have several direct clinical implications. First, the addition of sulodexide to alprostadil produced a synergistic antiproteinuric effect and a higher overall

response rate compared to alprostadil alone, supporting combination therapy as an effective option for elderly CKD patients who have persistent proteinuria despite monotherapy. Second, baseline Scr and UACR emerged as practical bedside thresholds with moderate predictive value; patients exceeding these values are at significantly higher risk of poor treatment response and may require more intensive monitoring, earlier consideration of alternative regimens, or combination therapy upfront rather than sequentially. Third, advanced age and diabetes mellitus were identified as independent risk factors for treatment failure, emphasizing that elderly diabetic patients should be targeted for stricter metabolic control and earlier nephroprotective intervention. These findings provide actionable evidence for individualized treatment decisions in this understudied population.

This study has several limitations that should be noted. The use of a retrospective, single-center approach may introduce selection bias and restrict the ability to generalize findings to a wider population. Comparatively brief four-week follow-up period limits the evaluation of long-term outcomes, such as progression to end-stage renal disease, cardiovascular events, or mortality. The absence of a sulodexide monotherapy arm prevents definitive attribution of the observed benefits specifically to combination versus either agent alone. Additionally, the study population was exclusively elderly Chinese patients, and findings may not directly translate to other ethnic or age groups.

Future prospective, randomized controlled trials with extended follow-up are warranted to confirm these findings and establish optimal treatment durations. Investigation of whether baseline biomarker thresholds can guide patient selection for combination therapy represents a promising avenue for personalized medicine approaches. Exploration of higher or escalated dosing regimens, as well as combinations with other renoprotective agents such as angiotensin-converting enzyme inhibitors or sodium-glucose cotransporter-2 inhibitors, may further enhance outcomes. Mechanistic studies examining the molecular basis of synergy between alprostadil and sulodexide could inform development of even more effective therapeutic strategies for elderly patients with CKD.

Beyond pharmacological interventions, innovative drug delivery strategies have also been explored in other studies to reduce nephrotoxicity while preserving therapeutic efficacy. For example, albumin nanoparticle-based formulations have been successfully used to redirect drug biodistribution away from the kidney, thereby mitigating renal injury [36]. Such approaches may be combined with combination pharmacotherapy in the future, to highlight the importance of multi-faceted renoprotective strategies in vulnerable populations such as elderly CKD patients.

Conclusion

Alprostadil combined with sulodexide improves renal function and clinical efficacy in elderly patients with CKD compared to alprostadil monotherapy. Age, diabetes mellitus, baseline Scr, and baseline urinary albumin-to-creatinine ratio are independent risk factors for poor therapeutic response, while combination therapy serves as a protective factor. Baseline Scr and urinary albumin-to-creatinine ratio demonstrate moderate predictive value for treatment outcomes and may assist in identifying patients who could benefit from more intensive therapeutic strategies. These findings support the use of combination therapy in appropriate elderly CKD patients and highlight the importance of early intervention before advanced renal damage becomes established.

Disclosure of conflict of interest

None.

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