Beraprost Sodium Delays the Decline of Glomerular Filtration Rate in Patients with Diabetic Nephropathy: A Retrospective Study

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ABSTRACT

Introduction: To investigate the reno-protective effect of beraprost sodium (BPS) in patients with diabetic nephropathy (DN).

Methods: We retrospectively analyzed patients with DN hospitalized in China-Japan Friendship Hospital from January 2015 to December 2021 who received combination of conventional treatment and BPS (120 ug/day) therapy. We selected patients with DN matched in age and estimated glomerular filtration rate (eGFR) as controls, who received only conventional therapy. Baseline information and clinical variables at each follow-up visit were collected from all patients. The changes of clinical variables were compared between the two groups before and after treatment.

Results: A total of 50 patients with DN met the inclusion and exclusion criteria, with 25 patients in each group. The baseline characteristics of the two groups have no significant difference ($p > 0.05$). Serum albumin levels after treatment were improved in both groups, but the improvement was statistically significant only in BPS group (35.5–39.8 g/l, $p < 0.001$). The eGFR worsened significantly in both groups ($p = 0.009$ and $p = 0.001$). However, the decline of eGFR was less in BPS group than that in control group (-9.8 vs. -16.7 ml/min/ 1.73 m^2, $p = 0.037$). In the subgroup analysis, 30 patients received 3–12 months treatment and 20 patients received more than 12 months treatment. During the 3–12 months treatment period, serum creatinine and eGFR in the control group were significantly worsened compared with those before treatment ($p = 0.019$ and $p = 0.03$), but in the BPS group they were relatively stable ($p > 0.05$). After more than 12 months treatment, although the serum creatinine and eGFR were significantly worsened in both groups ($p < 0.05$), the decline of eGFR was less in BPS group than that in control group (-10.1 vs. -25.9 ml/min/1.73 m^2, $p = 0.045$).

Conclusions: Combination of conventional treatment and BPS therapy delays the decline of eGFR in patients with DN in the long term.

Keywords: Beraprost sodium; Diabetic nephropathy; Glomerular filtration rate

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Key Summary Points

Diabetic nephropathy has become the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide.

Although possible beneficial roles for beraprost sodium (BPS) in DN have been suggested by animal studies, there have been few clinical studies investigating the renoprotection of BPS in patients with DN.

In this study, we retrospectively analyzed patients with DN who received combination of conventional treatment and BPS therapy to investigate the renoprotective effect of BPS.

Combination of conventional treatment and BPS therapy could delay the decline of eGFR in patients with DN.

INTRODUCTION

Diabetic nephropathy (DN), as one of the most common and serious microvascular complications of diabetes, has become the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [1]. Zhang showed that since 2011, DN has exceeded chronic glomerulonephritis in both general population and hospitalized urban population with CKD in China [2].

Due to the complex pathogenesis of DN [3], only a few breakthroughs have been made in the prevention and treatment of DN. International guidelines for the management of DN recommend control of blood glucose, blood pressure, blood lipids and other risk factors. The only classes of medicine that have been shown to slow DN progression were renin-angiotensin-aldosterone system (RAAS) inhibitors [4, 5] and sodium-glucose cotransporter 2 (SGLT2) inhibitors [6]. However, the clinical application of

RAAS and SGLT2 inhibitors is limited by the glomerular filtration rate. The prevalence of DN and the rates of ESRD have remained stable or decreased only slightly [7]. Therefore, the search for new pathogenesis and therapeutic target of DN is the focus of current research.

Beraprost sodium (BPS), as a stable, orally active prostacyclin (prostaglandin I_2 [PGI$_2$]) analog, can inhibit platelet activation, dilate microvessels and improve blood flow [8]. Some clinical cohort studies have shown that BPS was used to treat arteriosclerosis obliterans in patients with diabetes [9]. Possible beneficial roles for BPS in DN also have been suggested by some animal studies [10–12]. However, there have been few clinical studies about the reno-protection of BPS in patients with DN.

In this study, we retrospectively analyzed patients with DN who received combination of conventional treatment and BPS therapy to investigate the renoprotective effect of BPS.

METHODS

Subjects

The study protocol was in accordance with the Declaration of Helsinki (1964) and was approved by the Ethics Committee of China-Japan Friendship Hospital (2018-45-K34). All individuals included in this study had signed consent forms during hospitalization so that their information could be stored in the hospital database and used for research.

We retrospectively analyzed patients with DN hospitalized in the Department of Nephrology, China-Japan Friendship Hospital, from January 2015 to December 2021, who received conventional treatment or the combination of conventional treatment and BPS (Beijing Tide Pharmaceutical Co., Ltd., China, drug specification: 40 ug) three times per day of therapy. All patients enrolled in this study met the following inclusion and exclusion criteria. The inclusion criteria were as follows: (1) patient age was $\geq$ 18 years and $\leq$ 75 years; (2) patients were diagnosed with DN according to renal biopsy or clinical diagnostic criteria; (3) patients with regular follow-up every

2–3 months and at least 3 months treatment. The exclusion criteria were as follows: (1) patients with type 1 diabetes mellitus; (2) patients with an estimated glomerular filtration rate (eGFR) < 15 ml per minute per 1.73 m^2 of body-surface area; (3) patients with other primary or secondary glomerular diseases at the same time; (4) patients with acute kidney injury or diabetes mellitus acute complications; (5) patients with abnormal liver function.

Patients received combinational therapy with conventional treatment and BPS therapy were named as BPS group. Patients matched in age and eGFR to those in the BPS group were selected as controls. Patients in the control group received only conventional treatment. The conventional treatment mainly contained anti-diabetes and antihypertensive medications. If the patient had no contraindications, RAAS inhibitor had to be added. Since this was a retrospective study, the dosage of RAAS inhibitor for each patient may have been different, and the specific dosage was based on individual conditions such as the blood pressure. Hypoglycemic agent cannot include SGLT2 inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonists. Some patients may also use lipid-lowering drugs and uric-lowering drugs. No other oral medication with a proven renal protective effect was used in any enrolled patients.

Follow-up

The treatment period was at least 3 months. All patients visited the outpatient every 2–3 months during the follow-up period. At baseline, clinical data, such as age, duration of diabetes, serum levels of albumin (ALB), creatinine (Scr), blood urea nitrogen (BUN), uric acid level (SUA), and fasting blood glucose (FBG), and 24-h urinary protein concentration (24-h UP), were collected from all patients. During follow-up, these clinical variables were measured every 2–3 months in each person, and the renal function decline during follow-up was represented by the decline of eGFR. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The primary endpoints were ESRD or death. ESRD was defined as the initiation of chronic dialysis or eGFR < 15 ml/min/1.73 m^2.

Statistical Analyses

For continuous variables, baseline and follow-up data are reported as median (inter-quartile range [IQR]). Categorical variables are presented as count (*n*) and percentage (%). Comparisons between before and after treatment in each group were done using a paired t-test or Wilcoxon signed rank test. The change in variables was compared between groups using independent-samples non-parametric Mann-Whitney *U* test. All statistical tests were two-sided, and *p* values < 0.05 were considered statistically significant. All of the statistical analyses described above were performed using Statistical Package for Social Sciences version 22.0 (SPSS, IBM Corp, Armonk, NY).

RESULTS

From January 2015 to December 2021, 68 patients with DN received the combination of conventional treatment and BPS therapy in China-Japan Friendship Hospital. Of these patients, 43 were excluded because 9 patients were aged > 75 years old, 3 patients had other glomerular diseases, and 10 patients had eGFR < 15 ml/min/1.73 m^2 at baseline; 21 patients discontinued seeing the physician after their discharge. Thus, a total of 25 patients finally met the criteria for inclusion and exclusion and were named BPS group. Twenty-five patients with DN matched in age and eGFR with those in the BPS group were selected as controls, who received only conventional treatment. Thus, 50 patients with DN were included in the study, with 25 patients in each group. Of the 50 patients with DN, 38 patients were diagnosed by renal biopsy and 12 by clinical diagnostic criteria (Fig. 1).

Table 1 shows the baseline characteristics of all 50 enrolled subjects before treatment. Of these 50 patients with DN, 30 were treated for 3–12 months and 20 patients for > 12 months. The median age of the all patients was 58 (49–64) years. Comparisons of the baseline
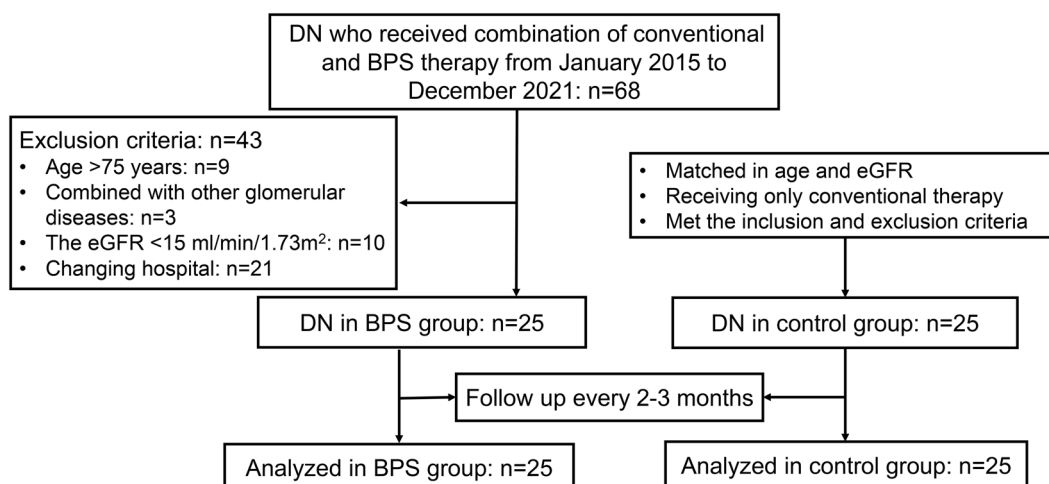
Fig. 1 Flowchart of study participants. *DN* diabetic nephropathy, *eGFR* estimated glomerular filtration rate, *BPS* beraprost sodium

Table 1 Baseline characteristics of subjects in the two groups

Variables	Overall ($n = 50$)	BPS group ($n = 25$)	Control group ($n = 25$)	p
Age (years)	58 (49−64)	56 (50.5−65.0)	60 (49−63)	0.377
Duration of diabetes (years)	11.5 (9.5−18.0)	12 (10.0−17.5)	10 (7−18)	0.458
ALB (g/l)	34.1 (30.0−39.3)	35.5 (29.3−40.0)	33.8 (30.8−37.8)	0.567
Scr (μmol/l)	125.5 (104.5−193.2)	124.2 (104−194)	125.6 (108.0−167.0)	0.992
BUN (mmol/l)	8.5 (6.4−11.3)	8.9 (6.8−12.0)	8.3 (6.2−10.6)	0.548
eGFR (ml/min/1.73m^2)	49.5 (31.6−69.5)	46.6 (29.9−69.7)	49.9 (30.1−66.2)	0.684
SUA (mmol/l)	395 (315.5−451.0)	376 (314.8−449.8)	400 (327−477)	0.582
FBG (mmol/l)	6.4 (4.8−8.9)	6.9 (4.6−9.1)	6.2 (5.0−8.6)	0.846
24-h UP (g/d)	3.3 (1.8−6.8)	2.4 (0.9−6.8)	4.1 (2.9−6.8)	0.119

BPS beraprost sodium, *ALB* serum albumin, *Scr* serum creatinine, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *SUA* serum uric acid, *FBG* fasting blood glucose, *24-h UP* 24-h urinary protein concentration

characteristics in both BPS and control groups were done, and there was no significant difference in any baseline characteristic (age, duration of diabetes, 24-h UP, ALB, Scr, BUN, SUA, FBG and eGFR) between the two groups.

Changes in biochemical variables after treatment in each group are shown in Table 2. The ALB levels were improved in both BPS and control groups, but the change was statistically significant only in BPS group (35.5–39.8 g/l,

$p < 0.001$). The 24-h UP was aggravated in both groups, but the change has no significant difference. Scr, BUN and eGFR worsened significantly in both groups ($p < 0.05$, Table 2). However, the decline was less in BPS group than in control group ($- 9.8$ vs. $- 16.7$ ml/min/1.73 m^2, $p = 0.037$, Table 3).

We additionally performed subgroup analysis at different treatment time points as shown in Tables 2 and 3. During 3–12 months of

Table 2 Comparison of variables between before and after treatment in each group

Variables	BPS group			Control group		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Whole cohort	n = 25			n = 25		
ALB (g/l)	35.5 (29.3−40.0)	39.8 (31.1−44.3)	0.001	33.8 (30.8−37.8)	35.9 (29.4−39.8)	0.404
Scr (μmol/l)	124.2 (104−194)	162.9 (112.1−298.5)	0.008	125.6 (108−167)	239.6 (143−491)	0.001
BUN (mmol/l)	8.9 (6.8−12.0)	9.8 (6.8−18.4)	0.037	8.4 (6.2−10.6)	13.8 (10.1−20.2)	0.001
eGFR (ml/min/ 1.73m^2)	46.6 (30.0−69.7)	36.9 (17.5−56.9)	0.009	49.9 (30.1−66.2)	27.7 (10.3−38.5)	0.001
SUA (mmol/l)	376 (314.8−449.8)	372.5 (307−433)	0.597	400 (327−477)	415 (321−469)	0.798
FBG (mmol/l)	6.95 (4.6−9.1)	7.81 (6.0−10.2)	0.137	6.2 (5.0−8.6)	7.72 (5.2−8.8)	0.150
24-h UP (g/d)	2.4 (0.9−6.8)	2.6 (1.1−5.3)	0.339	4.1 (2.9−6.8)	5.0 (2.5−6.6)	0.367
Treatment ≤ 12 months	n = 17			n = 13		
ALB (g/l)	35.5 (28.1−41.7)	39.9 (31−44.3)	0.005	33.8 (27−38.8)	36.9 (27.3−41.9)	0.311
Scr (μmol/l)	173 (109−215)	163 (125−409)	0.088	152 (113−269)	213 (131−556)	0.019
BUN (mmol/l)	8.9 (7.1−12.8)	10.3 (6.2−22.2)	0.113	10.4 (6.0−14.0)	7.9 (5.7−8.8)	0.004
eGFR (ml/min/ 1.73m^2)	40.4 (28.1−66.9)	38.3 (17.5−65.4)	0.084	45 (21.9−59.5)	27.7 (9.5−50.8)	0.03
SUA (mmol/l)	354 (310.5−436.0)	346 (296−384)	0.435	400 (328−510)	382 (296−478)	0.507
FGB (mmol/l)	7.6 (4.7−10.2)	7.2 (5.6−10.2)	0.906	6.8 (4.7−8.8)	7.9 (5.7−8.8)	0.221
24-h UP (g/d)	2.4 (1.3−7.2)	3.1 (0.9−6.7)	0.433	4.0 (2.2−7.5)	3.9 (1.2−7.3)	0.917
Treatment > 12 months	n = 8			n = 12		
ALB(g/l)	36.1 (29.9−38.8)	40 (31.8−44.3)	0.018	33.9 (31.6−34.8)	34.8 (30.9−37.2)	0.931
Scr (μmol/l)	108 (90−162)	188.1 (97−298)	0.05	120 (102−126)	278 (183−469)	0.002
BUN (mmol/l)	9.0 (5.9−10.7)	9.6 (7.8−12.8)	0.263	8.1 (6.4−8.8)	13.8 (11.0−18.8)	0.004
eGFR (ml/min/ 1.73m^2)	52.6 (36.6−79.6)	31.5 (15.1−52.3)	0.05	58.8 (50.4−75.1)	20.6 (12.3−33.9)	0.002
SUA (mmol/l)	450 (385−458)	446 (387−504)	0.735	397 (318−456)	431 (319−459)	0.754

Table 2 continued

Variables	BPS group			Control group		
	Before treatment	After treatment	p	Before treatment	After treatment	p
FGB (mmol/l)	6.8 (4.5−8.0)	9.4 (8.2−10.3)	0.028	5.9 (5.0−8.9)	6.4 (4.7−10.0)	0.347
24-h UP (g/d)	2.2 (0.7−6.1)	1.6 (1.1−3.5)	0.611	4.4 (3.1−6.1)	5.4 (4.5−6.6)	0.239

BPS beraprost sodium, *ALB* serum albumin, *Scr* serum creatinine, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *SUA* serum uric acid, *FBG* fasting blood glucose, *24-h UP* 24-h urinary protein concentration

treatment, ALB levels were improved in both BPS and control groups, but the change was statistically different only in BPS group ($p = 0.005$, Table 2). The Scr, BUN and eGFR were significantly worsened in the control group ($p < 0.05$, Table 2), but in the BPS group these three variables were relatively stable ($p > 0.05$, Table 2). After > 12 months of treatment, both Scr and eGFR were significantly worsened in both BPS and control groups ($p < 0.05$, Table 2). However, the decline of the eGFR was less in the BPS group than in control group ($- 10.1$ vs. $- 25.9$ ml/min/1.73 m^2, $p = 0.045$, Table 3).

DISCUSSION

In the present study, we retrospectively analyzed the long-term efficacy of BPS on the progression of renal function in patients with DN. We found that, although eGFR worsened in the both BPS and control groups over the study period, the decline of eGFR in BPS group was less than that in the control group after a long-term treatment.

The pathogenesis of DN is complex and involves a multitude of different pathways, such as metabolic disturbance, hemodynamic changes, inflammation and genetic factors [3]. For this reason, although many medications have been recommended for the treatment of DN, the prevalence of DN and the rate of ESRD have remained stable or decreased only slightly. The use of RAAS inhibitors is the traditional treatment for DN, which can reduce urinary protein and delay the deterioration of renal function

[5]. However, dry cough, hyperkalemia and acute kidney injury limited its clinical use for DN treatment. More recently, some novel hypoglycemic agents, including GLP-1 receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors and SGLT-2 inhibitors, have attracted increasing attention [13]. For example, SGLT2 inhibitors can reduce the reabsorption of glucose and sodium in proximal renal tubules and relieve the hyperperfusion and hyperfiltration of glomerulus [6]. Although SGLT2 inhibitors have been proven to prevent the progression of DN and reduce the risk of cardiovascular disease [14], the side effects including low blood pressure, urinary system and reproductive system infection risk, acute kidney injury and ketoacidosis cannot be ignored [15]. Therefore, the search for new pathogenesis and therapeutic target of DN is a hotspot.

Prostaglandins, such as alprostadil and BPS, were widely used in the clinic treatment of DN based on their vasodilatory and anti-platelet effects. Clinical studies have shown that alprostadil can reduce proteinuria and prevent the progression of DN [16, 17]. Possible beneficial roles for BPS in DN also have been suggested by some animal studies [10–12]. However, there were few clinical studies about the kidney-protective effect of BPS in patients with DN. Therefore, we designed this study to assess the long-term efficacy of BPS on the progression of renal function in patients with DN, and our results demonstrated the renoprotection of BPS treatment, which was consistent with previous studies.

The mechanism and related pathways of renoprotection of prostaglandins remain

Table 3 Assessment by calculation of differences between final and initial values at different treatment time points between the two groups

Variables	BPS group	Control group	p
Whole cohort	$n = 25$	$n = 25$	
ALB (g/l)	3.7 (1.1−5.9)	1.7 (− 2.7−4.5)	0.066
Scr (μmol/l)	18.6 (− 1.7−129.7)	126.7 (13.5−288.2)	0.069
BUN (mmol/l)	1.3 (− 1.2−7.0)	5.7 (2.8−10.3)	0.021
eGFR (ml/min/1.73m^2)	− 9.8 (− 12.3−0.6)	− 16.7 (− 33.9−5.0)	0.037
SUA (mmol/l)	− 28 (− 72.5−57.5)	− 14 (− 112−99)	0.912
FGB (mmol/l)	0.8 (− 0.8−2.6)	0.9 (− 1.1−3.7)	0.795
24-h UP (g/d)	− 0.7 (− 3.4−0.9)	0.2 (− 1.6−2.7)	0.074
Treatment ≤ 12 months	$n = 17$	$n = 13$	
ALB (g/l)	2.7 (1.1−4.8)	3.1 (− 1.8−5.8)	0.759
Scr (μmol/l)	15.1 (− 8.2−160)	32.2 (− 2.1−254.3)	0.405
BUN (mmol/l)	1.3 (− 1.5−10.8)	4.0 (2.0−10.7)	0.127
eGFR(ml/min/1.73m^2)	− 5.6 (− 12.3−2.9)	− 8.4 (− 13.7−0.7)	0.754
SUA (mmol/l)	− 34 (− 75.5−55.0)	− 42 (− 112.0−77.5)	0.818
FGB (mmol/l)	0.3 (− 2.1−1.8)	0.9 (− 1.1−3.7)	0.346
24-h UP (g/d)	− 0.7 (− 3.6−0.6)	− 0.4 (− 1.6−3.2)	0.322
Treatment > 12 months	$n = 8$	$n = 12$	
ALB (g/l)	5.9 (1.9−7.4)	0.7 (− 3.8−3.8)	0.015
Scr (μmol/l)	46.2 (1.3−129.7)	142.1 (56.9−367.8)	0.165
BUN (mmol/l)	1.4 (− 0.8−3.7)	7.5 (2.8−10.3)	0.076
eGFR (ml/min/1.73m^2)	− 10.1 (− 37.2−1.7)	− 25.9 (− 64.3−20.9)	0.045
SUA (mmol/l)	17 (− 65−99)	21(− 113.5−153)	0.933
FGB (mmol/l)	1.4 (− 0.8−3.7)	1.2 (− 1.3−5.0)	0.272
24-h UP (g/d)	− 0.4 (− 3.3−0.9)	0.7 (− 3.8−3.8)	0.165

BPS beraprost sodium, *ALB* serum albumin, *Scr* serum creatinine, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *SUA* serum uric acid, *FBG* fasting blood glucose, *24-h UP* 24-h urinary protein concentration

unclear. In a prospective study of patients with chronic glomerulonephritis, prostaglandins maintained renal plasma flow and alleviated the progression of renal insufficiency [18]. In a randomized study of patients with aristolocholic acid nephropath, a typically tubulointerstitial disease, prostaglandin therapy slowed the progression of renal failure [19]. This finding indicates that the target of prostaglandins might be tubulointerstitial lesions rather than glomerular injury. In fact, DN is traditionally considered to be a primarily glomerular disease, but this contention has been recently challenged [20]. Only one third of patients with

type 2 diabetes and microalbuminuria have typical glomerulopathy, and the others have minor or no glomerular changes, but disproportionately severe tubulointerstitial lesions [21]. These findings indicate that the tubulointerstitium injury might be an important early event in the pathogenesis of DN. In our study, we found that BPS delayed the decrease of eGFR in patients with DN, and we speculated that the underlying mechanism might be the improving of tubulointerstitial lesions. Based on the network pharmacology study, our team also found that prostaglandins may play a protective role in DN through the hypoxia-inducible factor-1 (HIF-1) pathway.

Indeed, the kidneys are the second highest oxygen consumers in the body, and sustained hyperglycemia will result in increased oxygen consumption and decreased intrarenal oxygenation, suggesting that the diabetic kidney is more likely to develop hypoxia [22]. Hypoxia in DN has been previously described and is likely an early event in diabetes [23, 24]. Increasing evidence suggests that tubulointerstitial hypoxia in diabetes might be an important event in the early stage and plays an important pathophysiologic role in the progression of DN [20]. Prostaglandin is widely used in the clinic because it can dilate blood vessels and improve peripheral circulation, which may improve tubulointerstitial hypoxia and injury. Further animal experiments are needed to confirm this mechanism.

The limitation of the current study was the relatively small sample size, especially in the subgroup analysis, which may affect the detection of some statistically significant changes. For instance, there was a tendency of improvement of 24-h urinary albumin excretion in BPS group after 12 months of treatment, but no statistical difference. Second, not all enrolled patients with DN were diagnosed by renal biopsy. Third, combined medications like diabetes medications which can affect primary outcomes were not controlled during treatment. Fourth, the blood pressure data during the follow-up were incomplete. Further studies with a larger number of patients and a longer observation period are needed to confirm the renoprotection effect of BPS.

CONCLUSIONS

In conclusion, the current study demonstrated that BPS therapy attenuated the decline of eGFR in patients with DN in the long term. Therefore, recommendations for treatment of patients with DN may also include improving kidney microcirculation. More high-quality studies with large samples are needed to confirm our conclusion.

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could be stored in the hospital database and used for research. The study was performed in accordance with the Helsinki Declaration of 1664 and its later amendments.

Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding authors on reasonable request.

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