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Beraprost Sodium Protects Against Diabetic Nephropathy in Patients with Arteriosclerosis Obliterans: A Prospective, Randomized, Open-label Study

Ayaka Shima, Masaaki Miyamoto, Yoshiaki Kubota,
Gen Takagi and Wataru Shimizu

Department of Cardiovascular Medicine, Nippon Medical School

Background: Inhibition of the renin-angiotensin system (RAS) has been used to treat diabetic nephropathy. However, RAS inhibition increases the risk of renal complications. In this study, we evaluated the effect of combining RAS inhibitor treatment with beraprost sodium (BPS), a prostaglandin I_2 analog, in diabetic nephropathy with arteriosclerosis obliterans.

Methods: This study was a prospective, randomized, open-label study. Twenty-six Japanese patients (age >30 years) with diabetic nephropathy and arteriosclerosis obliterans were randomly assigned to the BPS group (n=13), which received the combination of an RAS inhibitor and BPS (120 μg/day) therapy, or the control group (n=13), which received only an RAS inhibitor. Patients were followed up for 1 year. The primary endpoint was the effect of BPS on renal function.

Results: In the control group, serum creatinine (1.64±0.87 to 2.34±1.53 mg/dL, $p<0.001$), 1/creatinine (0.82±0.47 to 0.65±0.47, $p=0.003$) cystatin C (1.77±0.61 to 2.18±0.86 mg/L, $p<0.001$), and the estimated glomerular filtration rate (43.9±26.1 to 34.0±24.6 mL/min/1.73 m^2, $p=0.004$) were significantly worsened 48 weeks after the start of treatment. Conversely, in the BPS group, serum creatinine (1.71±0.75 to 1.66±0.81 mg/dL, $p=0.850$), 1/creatinine (0.66±0.19 to 0.71±0.25, $p=0.577$), cystatin C (1.79±0.55 to 1.80±0.57 mg/L, $p=0.999$), and the estimated glomerular filtration rate (35.8±10.8 to 38.7±14.4 mL/min/1.73 m^2, $p=0.613$) were unchanged.

Conclusions: Combination treatment with BPS and an RAS inhibitor prevented the progression of diabetic nephropathy. These observations should be confirmed in large-scale studies with long-term follow-up. (J Nippon Med Sch 2015; 82: 84–91)

Key words: beraprost sodium, renin-angiotensin system inhibitor, diabetic nephropathy, cystatin C

Introduction

The number of patients undergoing hemodialysis for end-stage renal disease (ESRD) in Japan increases every year[1]. The most common cause of ESRD in Japan, representing approximately 40% of cases[2], is diabetic nephropathy[3]. Inhibitors of the renin-angiotensin system (RAS) have shown benefits in the treatment of diabetic nephropathy[4–8]. Moreover, several clinical trials indicate that the effect of RAS inhibitors is dose-dependent[9] and is associated with a reduced progression rate to overt nephropathy, remission of microalbuminuria to normoalbuminuria, and regression of the urinary albumin-to-creatinine ratio (UACR)[10–12].

Nevertheless, single-agent therapies do not fully block the RAS, and patients treated with these agents remain at high risk for renal complications. Thus, the optimal treatment approach requires an increase in the RAS inhibitor dosage. However, increasing the inhibitor dosage can be difficult when the patient has hypotension or hyperkalemia or both. Furthermore, renal vascular resistance increases as thromboxane A_2 (TXA_2) accumulates in diabetic nephropathy, thereby enhancing platelet aggregation and promoting vasoconstriction[13]. Thus, decreased renal plasma flow (RPF) causes increased platelet aggregation in the renal glomerulus[14].

Prostacyclin (prostaglandin I_2 [PGI_2]) analogs prevent

Correspondence to Masaaki Miyamoto, MD, PhD, Department of Cardiovascular Medicine, Nippon Medical School, 1−1−5 Sendagi, Bunkyo-ku, Tokyo 113−8603, Japan
E-mail: miyamoto-m@nms.ac.jp
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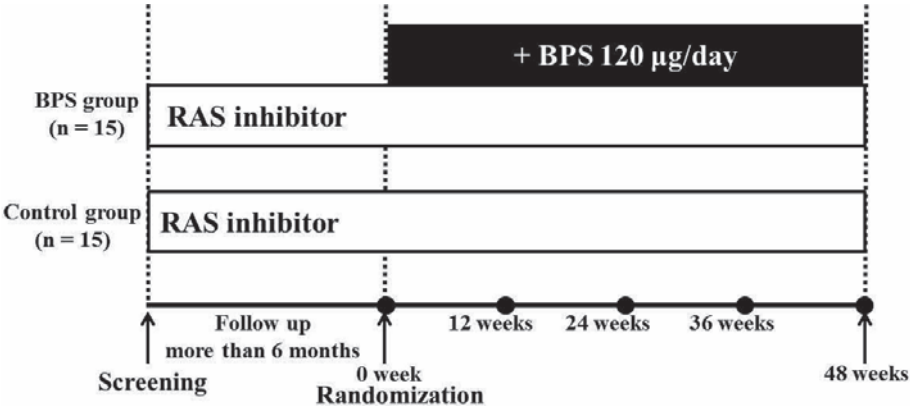

Fig. 1 Study design

Thirty patients were randomly assigned to the BPS group (15 patients), which received combination therapy with an RAS inhibitor and BPS (120 μg/day), or to the control group (15 patients), which only received an RAS inhibitor. After randomization, the patients were followed up at weeks 0, 12, 24, 36, and 48.

BPS: beraprost sodium; RAS: renin-angiotensin system

glomerular hyperfiltration, reduce RPF by dilatation of afferent and efferent arterioles, and prevent the progression of diabetic nephropathy[15]. Recent studies have also shown that beraprost sodium (BPS), a PGI_2 analog used to treat arteriosclerosis obliterans (ASO), has renoprotective effects[16]. However, whether combination therapy with an RAS inhibitor and a PGI_2 analog can inhibit the progression of diabetic nephropathy remains unclear. Patients with diabetic nephropathy and ASO should avoid dialysis, because it worsens their prognosis[17]. The aim of this study was to evaluate the effect of combination therapy with an RAS inhibitor and a PGI_2 analog in patients with diabetic nephropathy and ASO.

Materials and Methods

Subjects

The subjects of this study were 30 patients older than 30 years with diabetic nephropathy and ASO. The ASO was diagnosed on the basis of a history of intermittent claudication, according to the guidelines of the TransAtlantic Inter-Society Consensus document II. Patients with diabetic nephropathy of stage 2, 3, or 4 were selected[18]. The subjects were receiving RAS inhibitor therapy and had not received BPS for at least 6 months. Patients with type 1 diabetes mellitus (DM), hemoglobin A1c (HbA1c) >8.0%, serum creatinine >3 mg/dL, and severe liver dysfunction were excluded.

The patients were randomly assigned to 1 of 2 groups. The BPS group (15 patients) received combination therapy with an RAS inhibitor and BPS (120 μg/day), whereas the control group (15 patients) received only the RAS inhibitor. The dose of BPS was not changed during the study period. This study was a prospective, randomized, open-label study, with randomization performed with a random number table. All patients were instructed to continue their normal diet and exercise therapy during the study. The study protocol was approved by the Ethics Committee of Nippon Medical School Hospital. All 30 subjects provided written informed consent before enrollment. Patients could discontinue therapy by their own free will after consent. This study was registered in the University Hospital Medical Information Network Clinical Trials registry as trial UMIN000010035.

Follow-up

After randomization, the clinical conditions and renal variables were evaluated at weeks 0, 12, 24, 36, and 48. The total treatment period was 48 weeks (**Fig. 1**). At baseline and follow-up, the blood pressure (BP), ankle-brachial index (ABI), and pulse wave velocity (PWV) were evaluated. Furthermore, clinical assessments were performed, and blood was sampled to evaluate compliance. Renal function was determined on the basis of serum creatinine, 1/creatinine, estimated glomerular filtration rate (eGFR), cystatin C, UACR, and urinary protein content. The control of DM was evaluated on the basis of HbA1c.

Evaluation of the Effectiveness of the BPS

The primary endpoint was improved renal function variables, including serum creatinine, 1/creatinine, cystatin C, eGFR, UACR, and urinary protein, in patients of the BPS compared with the control group. The secondary endpoints were the effects of BPS on hemodynamic vari-

ables associated with ASO, such as ABI and PWV, and the DM-associated variable HbA1c.

Measurement of Physiological Variables

Relevant clinicopathological factors

Blood samples were obtained from the antecubital vein after an overnight fast of at least 12 hours. The HbA1c was measured according to the National Glycohemoglobin Standardization Program (NGSP). The presence of DM was defined by HbA1c (NGSP) ≥6.5% or concomitant use of a hypoglycemic agent. The UACR (mg/g creatinine) was calculated as albumin concentration (mg/L) divided by creatinine concentration (g/L). The urinary concentrations of albumin and creatinine were determined with a turbidimetric immunoassay (Autokit Micro Albumin; Wako Pure Chemical Industries, Osaka, Japan) and with the Jaffe reaction using an autoanalyzer. The UACR measurement estimated the 24-hour urine albumin excretion. A single morning-voided urine sample at the baseline examination was used to measure the UACR. Cystatin C was measured with the latex agglutination turbidimetry method (Auto Cystatin C, BML Inc., Tokyo, Japan). The reference range, as described in the manufacturer's instructions, was 0.40 to 0.91 mg/L. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥140 mg/dL or concomitant use of a lipid-lowering agent. The glomerular filtration rate was estimated with the simplified prediction equation derived from the Modification of Diet in Renal Disease study[19].

BP, ABI, and PWV

The brachial BP was determined with oscillometry, with the patient in a seated position. The ABI and PWV were measured with the patient in the supine position after 5 minutes of rest by means of an automated polygraph device (AT-form PWV/ABI; Nippon Colin, Komaki, Japan). Measurements were taken from the heart to the dorsalis pedis or the posterior tibial artery to just above ankle and dividing the arterial length (estimated from patient's height) using the time lag between the second heart sound (aortic closure) and the dicrotic notch of arterial pressure. This device simultaneously records the phonocardiogram, electrocardiogram, volume pulse form, and arterial BP in both the left and right arms and the ankles[20]. Increased aortic stiffness was determined with the measurement of PWV[21]. The PWV is inaccurately low as the ABI is markedly decreased[22]. In contrast, PWV in ESRD increases despite decreased ABI[21]. The height and weight of the patients were measured at the time of ABI measurement, and the body-mass index (BMI; kg/m^2) was calculated as an index of obesity.

Statistical analysis

Statistical analysis was performed with the software package IBM SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA). The results are expressed as the mean± standard deviation. Serial changes in variables were evaluated with a repeated-measures two-way analysis of variance, followed by Scheffe's F-test or a paired Student's *t*-test, as appropriate. The change in variables was compared between groups using Student's *t*-test. A *p*-value <0.05 was considered significant.

Results

From April 2012 through June 2013, 32 patients agreed to participate in this study. Of these, 2 were excluded because the serum creatinine was >3 mg/dL. Of the 30 enrolled subjects, 4 were excluded. In the BPS group, 2 subjects were excluded because they discontinued seeing the physician. In the control group, 2 subjects were excluded because 1 died and the other changed hospitals. Thus, 26 patients completed the study, with 13 patients in each group (**Fig. 2**).

Table 1 shows the baseline characteristics of the study subjects before BPS treatment. The mean age of the patients was 67.3±10.7 years, and 23 subjects (88%) were male. The patients groups did not differ significantly in any baseline characteristic (age, sex, BMI, smoking, systolic BP [SBP], hypertension, dyslipidemia, renal function variables, DM-associated variables, or concomitant medication).

Changes in biochemical variables at baseline and after 48 weeks of treatment are shown in **Table 2 and 3**. Cystatin C, serum creatinine, 1/creatinine, and eGFR worsened significantly in the control group over the 48-week study period ($p<0.05$, **Table 2**). Conversely, these variables were unchanged in the BPS group (**Table 3**). Serum potassium, blood urea nitrogen (BUN), UACR, and PWV were unchanged in both groups (**Table 2 and 3**).

Figure 3 shows the serial changes in the SBP, cystatin C, serum creatinine, 1/creatinine, eGFR, and HbA1c at weeks 0, 12, 24, 36, and 48 in both groups. Interestingly, cystatin C, serum creatinine, and 1/creatinine significantly worsened at 36 and 48 weeks versus baseline in the control group ($p<0.05$) but not in the BPS group. The HbA1c decreased in the control group (6.92±0.54 to 6.44± 0.56%, $p=0.016$). Conversely, in the BPS group, these values remained unchanged (6.60±0.96 to 6.22±0.75%, $p=0.181$). The SBP did not change significantly during the follow-up period in either group.

The percentage increase in cystatin C was greater in

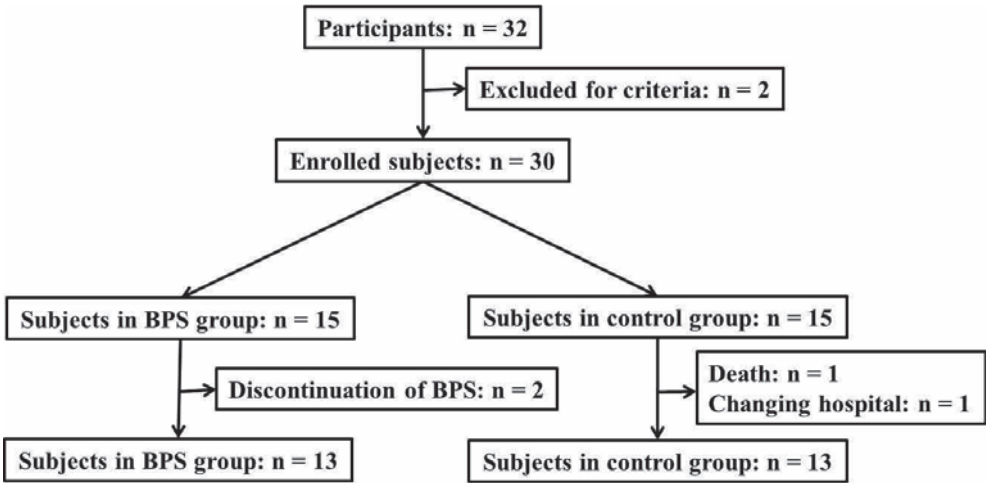

Fig. 2 Study enrollment

A total of 32 subjects were initially enrolled. Two patients were excluded because of established criteria. The study analyzed 13 patients receiving an RAS inhibitor alone (control group) and 13 patients receiving an RAS inhibitor and a PGI_2 analog (BPS group).

RAS: renin-angiotensin system; BPS: beraprost sodium

Table 1 Baseline characteristics

Variables	Beraprost sodium group (n=13)	Control group (n=13)	*p*-value
Age (years)	67.8±10.4	66.8±11.5	0.818
Male sex (%)	92.3	84.6	0.558
Body-mass index (kg/m²)	25.9±3.66	25.8±4.43	0.915
Smoking history (%)	46.2	61.5	0.452
Systolic blood pressure (mm Hg)	129.9±21.2	136.7±18.2	0.392
Coexisting condition			
Hypertension (%)	84.6	100	0.165
Dyslipidemia (%)	84.6	92.3	0.558
Medication use			
Calcium-channel blocker (%)	53.9	69.2	0.440
β-blocker (%)	23.1	38.5	0.416
Diuretic (%)	30.8	23.1	0.674
Insulin (%)	30.8	61.5	0.125
Spherical carbon adsorbent (%)	46.2	46.2	1.000
Serum potassium (mEq/L)	4.67±0.56	4.81±0.72	0.611
Blood urea nitrogen (mg/dL)	27.7±12.1	27.2±11.7	0.914
Creatinine (mg/dL)	1.71±0.75	1.64±0.87	0.824
1/Creatinine	0.66±0.19	0.82±0.47	0.276
Estimated glomerular filtration rate (mL/min/1.73 m²)	35.8±10.8	43.9±26.1	0.313
Cystatin C (mg/L)	1.79±0.55	1.77±0.61	0.918
Urine albumin (mg/g・Cr)	657.4±933.5	1,310.9±310.9	0.314
Urine protein (mg/dL)	133.6±218.0	171.1±233.4	0.675
Hemoglobin A1c (NGSP, %)	6.60±0.96	6.92±0.54	0.313
Ankle-brachial index	0.92±0.28	1.10±0.18	0.074
Pulse wave velocity	1,531.5±612.4	1,755.7±604.8	0.357

Plus-minus values are mean±S.D. or *n* (%). **p*<0.05, ***p*<0.01, ****p*<0.001, vs. baseline by paired Student's *t*-test, as compared with that before treatment.

the control group than in the BPS group (control group: 23.6±23.7; BPS group: 2.06±18.8, p=0.017, **Table 4**). Similar results were obtained for other renal functions (**Table 4**).

Table 2 Changes in the control group

Variables	Baseline	After 48 weeks	*p*-value
Systolic blood pressure (mm Hg)	136.7±18.2	132.2±18.7	0.943
Serum potassium (mEq/L)	4.81±0.72	4.75±0.76	0.998
Blood urea nitrogen (mg/dL)	27.2±11.7	34.7±20.4	0.216
Creatinine (mg/dL)	1.64±0.87	2.34±1.53	<0.001
1/Creatinine	0.82±0.47	0.65±0.47	0.003
Estimated glomerular filtratration rate (mL/min/1.73 m^2)	43.9±26.1	34.0±24.6	0.004
Cystatin C (mg/L)	1.77±0.61	2.18±0.86	<0.001
Urine albumin (mg/g・Cr)	1,310.9±2,066.4	749.5±938.0	0.530
Urine protein (mg/dL)	171.1±233.4	83.1±111.2	0.066
Hemoglobin A1c (NGSP, %)	6.92±0.54	6.44±0.56	0.016
Ankle-brachial index	1.10±0.18	0.94±0.34	0.600
Pulse wave velocity	1,755.7±604.8	1,720.9±574.9	0.989

Plus-minus values are mean±S.D. *p<0.05, **p<0.01, ***p<0.001, vs. baseline by repeated analysis of variance, as compared with before treatment.

Table 3 Changes in the beraprost sodium group

Variables	Baseline	After 48 weeks	*p*-value
Systolic blood pressure (mm Hg)	129.9±21.2	136.1±17.3	0.629
Serum potassium (mEq/L)	4.67±0.56	4.61±0.49	0.988
Blood urea nitrogen (mg/dL)	27.7±12.1	24.6±12.8	0.715
Creatinine (mg/dL)	1.71±0.75	1.66±0.81	0.850
1/Creatinine	0.66±0.19	0.71±0.25	0.577
Estimated glomerular filtratration rate (mL/min/1.73 m^2)	35.8±10.8	38.7±14.4	0.613
Cystatin C (mg/L)	1.79±0.55	1.80±0.57	0.999
Urine albumin (mg/g・Cr)	657.4±933.5	1,086.0±1,685.9	0.606
Urine protein (mg/dL)	133.6±218.0	117.8±158.0	0.980
Hemoglobin A1c (NGSP, %)	6.60±0.96	6.22±0.75	0.181
Ankle-brachial index	0.92±0.28	0.89±0.27	0.743
Pulse wave velocity	1,531.5±612.4	1,699.0±401.5	0.287

Plus-minus values are mean±S.D. *p<0.05, **p<0.01, ***p<0.001, vs. baseline by repeated analysis of variance, as compared with those before treatment.

Discussion

Our study has shown that treatment with the combination of BPS and an RAS inhibitor has a greater renoprotective effect than does treatment with an RAS inhibitor alone, which was confirmed by renal variables, including cystatin C, serum creatinine, 1/creatinine, and eGFR after 48 weeks of treatment. Furthermore, the SBP was not significantly changed in either group, indicating that BPS may contribute to renal protection independent of SBP.

Several previous studies have explained the renoprotective mechanism of BPS, a PGI_2 analog. Wang *et al*. have reported that BPS decreases microalbuminuria and rectified glomerular hyperfiltration in rats with early streptozotocin-induced diabetic nephropathy[13]. Moreover, Goto *et al*. have reported that BPS suppresses the structural regression of the renal microvascular network and decreases renal blood flow in the kidneys of rats with glomerulonephritis[23]. Our findings are supported by previously elucidated mechanisms. In patients with diabetic nephropathy, the afferent arterioles dilate more than do the efferent arterioles[14]. Thus, the glomerular pressure is elevated by the imbalance between the afferent and efferent arterioles, because dilation of the afferent arterioles induces glomerular hyperfiltration and hypertension[16]. The efferent arteriole is more sensitive to angiotensin II than is the afferent arteriole[24]. As a result, the efferent arteriole is more constricted. Angiotensin II receptor inhibitors and angiotensin-converting enzyme inhibitors, which dilate the efferent arteriole, decrease the glomerular pressure and induce a renoprotective response. Prostaglandins can alleviate angiotensin II-induced constriction of efferent arterioles *in vitro*[25].

BPS, a PGI_2 analog, dilates most arteries and arterioles via the PGI_2 receptor in the endothelial and vascular

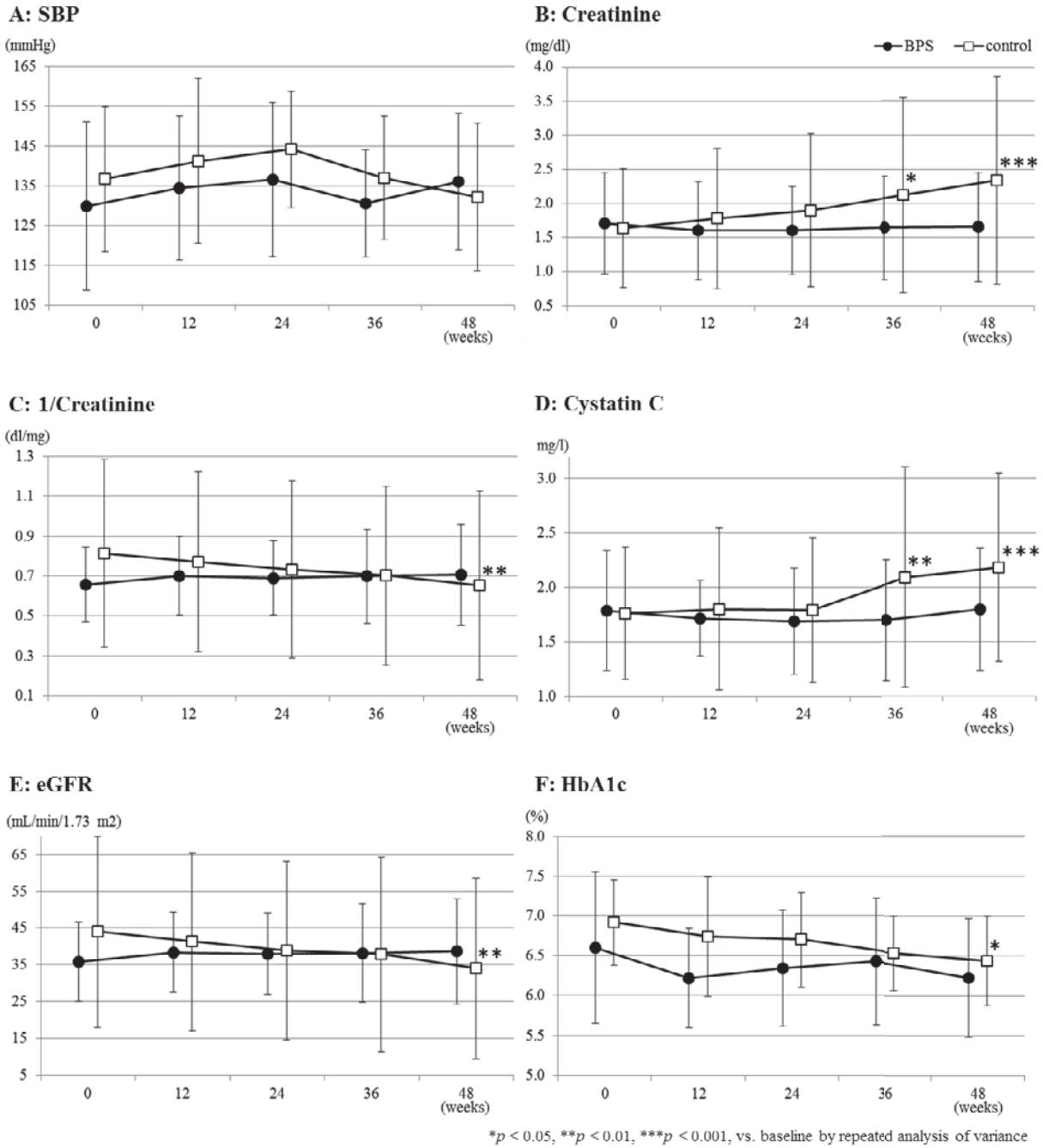

Fig. 3 Serial changes from baseline to 48 weeks in (A) SBP, (B) creatinine, (C) 1/creatinine, (D) cystatin C, (E) eGFR, and (F) HbA1c in the BPS and control groups
In the control group (n=13), cystatin C, serum creatinine, and 1/creatinine significantly worsened at weeks 36 or 48 or both (p<0.05); however, no differences were observed in the BPS group (n=13). The SBP was not significantly changed during the follow-up period in either group. The HbA1c was decreased in the control group (p<0.05) but not in the BPS group (p=0.181).
SBP: systolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c

smooth muscle cells[26,27]. Nitric oxide (NO), a vasodilator, may also dilate afferent arterioles[28,29]. In diabetic nephropathy, expression of endothelial nitric oxide synthase (eNOS) is increased in the afferent arterioles but not in the efferent arterioles. Thus, excessive NO can dilate afferent arterioles[30]. BPS is thought to suppress eNOS expression. Moreover, the prostacyclin receptor, which BPS acts upon, is highly expressed in the afferent arterioles but not in the efferent arterioles[31,32]. These results suggest that BPS suppresses glomerular hyperfiltration by suppressing NO production in afferent arterioles. In end-stage diabetic nephropathy, RPF gradually decreases. Re-

Table 4 Percentage changes in renal functions from baseline to 48 weeks in the beraprost sodium and control groups

Variables	Beraprost sodium group (%)	Control group (%)	*p*-value
Creatinine	–3.23±19.7	38.7±38.3	0.003
1/Creatinine	7.88±26.2	–22.5±21.6	0.004
Cystatin C	2.06±18.8	23.6±23.7	0.017
Estimated glomerular filtration rate	9.33±29.6	–24.4±23.3	0.004

Plus-minus values are mean±S.D. *p<0.05, **p<0.01, ***p<0.001, vs. baseline by paired Student's t-test, as compared with that before treatment.

portedly, BPS can preserve RPF and improve chronic kidney disease (CKD)[16,33]. Interestingly, glomerular hyperfiltration and increased renal blood flow can exacerbate CKD. Nevertheless, BPS does not increase glomerular filtration pressure, regardless of increased RPF.

Previous studies in animal models of CKD have suggested that the combination of BPS and telmisartan is more effective for reducing urinary albumin than are conventional RAS inhibitors[34]. In rats with diabetic nephropathy, cicaprost, a PGI_2 analog, decreases urinary albumin levels to the same extent as do angiotensin-converting enzyme inhibitors and alleviates diabetic renal injury by reducing the number of sclerotic glomeruli[35]. In our study, however, UACR was unchanged over the 48-week study period in both groups, likely because of the small number of subjects and because nephropathy was aggravated in 18 subjects. Furthermore, the significant decrease in HbA1c in the control group suggests that oral antidiabetic drugs were added and that the insulin dosage was increased in the control group versus the BPS group.

Our findings suggest that BPS is renoprotective in patients with diabetic nephropathy.

Strengths and Limitations of This Study

The present study is, to our knowledge, the first to show that combination therapy with an RAS inhibitor and a PGI_2 analog improves the symptoms of diabetic nephropathy. However, our study was limited by the use of a single hospital and the small number of patients. The patients were randomly assigned to treatment groups, but they were not treated in a blinded manner. We hypothesize that urine protein levels showed no significant change because of the small number of subjects, and it remains unclear whether BPS reduces albuminuria. Thus, because of selection bias these observations must be confirmed in a large renal function outcome study with long-term follow-up.

Conclusions

The results of the present study suggest that the combination of BPS and an RAS inhibitor prevents the progression of diabetic nephropathy.

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