Effect of Long-Term Administration of Prostaglandin I₂ in Incipient Diabetic Nephropathy

Akira Owada Shin Suda Toshihiko Hata

Department of Internal Medicine, Musashino Red Cross Hospital, Tokyo, Japan

Key Words

Type 2 diabetes mellitus · Microalbuminuria · Beraprost sodium · Hypertension · Protein intake

Abstract

Background/Aims: Diabetic nephropathy is one of the primary diseases of refractory renal failure and heads the list of patients undergoing dialysis. Therefore, it is very important to get treatment in incipient nephropathy. **Methods:** Twenty-seven patients in incipient diabetic nephropathy of type 2 diabetes mellitus who showed signs of microalbuminuria were randomly, but not blindly, assigned to two groups, either the beraprost sodium (PGI₂) group or the control group, and effects of the preparation on urinary albumin excretion or other parameters were examined for 24 months. **Results:** Urinary albumin excretion was significantly decreased after 18 months in beraprost sodium group; however, there was no change in the control group. Difference was observed between the two groups after month 12; however, it was not significant ($p = 0.0673$ at month 24). Three factors that affect urinary albumin excretion, e.g. blood pressure, blood sugar and protein intake, were almost constant during the study period. The level of creatinine

clearance was significantly decreased in beraprost sodium group after 24 months as compared with the control group. **Conclusion:** In this study, we found that the long-term 24-month administration of PGI₂ preparation, beraprost sodium, decreased albuminuria in patients of incipient diabetic nephropathy. The possible mechanisms are that the PGI₂ may have alleviated constriction effect of angiotensin II on efferent glomerular arteriole and attenuated glomerular hyperfiltration, and inhibited growth of mesangial cells by platelet-derived growth factor as well.

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Introduction

Diabetic nephropathy is one of the primary diseases of refractory renal failure and heads the list of patients undergoing dialysis, and it accounts for nearly 35% in Japan and North America. It is very important to start treatment in early stage of the nephropathy; however, any effective drugs other than angiotensin-converting enzyme inhibitors (ACE-I) have not been reported.

The typical histological structure of diabetic nephropathy is expansion of mesangial cells and their matrix, and it

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0028-2766/02/0924-0788\$18.50/0

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Akira Owada
1-26-1 Kyonan-cho
Musashino-city 180-8610, Tokyo (Japan)
Tel. +81 422 32 3111, Fax +81 422 32 9551

is represented as hypertrophy of the glomerular basement membrane as well. As one of the factors for these morphological changes that were observed in the incipient nephropathy, growth factors or cytokines have been suggested to have some relationship, one of which is platelet-derived growth factor (PDGF). The PDGF was found to be released from platelets as a growth factor of vascular smooth muscle cells; however, it has been revealed to be produced in mesangial cells. It has also been shown experimentally that the growth of mesangial cells was stimulated by PDGF, and production of collagen by mesangial cells was prevented by neutralizing antibody of PDGF [1]. The beraprost sodium was shown to inhibit PDGF (10 ng/ml)-induced DNA synthesis significantly in a dose-dependent manner in cultured smooth muscle cells derived from the thoracic aorta of a rabbit when concentration was greater than 30 nM [pers. commun., Eiji Ohmori]. This indicates the PDGF-induced growth of vascular smooth muscle cells is inhibited by beraprost sodium. As mesangial cells are similar in character to vascular smooth muscle cells, beraprost sodium may have similar effects to inhibit PDGF-induced mesangial cell growth and consequently protect the aggravation of diabetic nephropathy.

It has been suggested that glomerular hyperfiltration has been strongly involved in progression of disease in incipient diabetic nephropathy, and the mechanism is mainly due to the increased intraglomerular pressure caused by constriction effect of angiotensin II on efferent glomerular arteriole. The efficacy of ACE-I to protect progression of incipient diabetic nephropathy is due to an adjustment of the intraglomerular pressure [2]. Recently, it was shown that prostaglandins alleviated angiotensin II-induced constriction of efferent glomerular arteriole in vitro [3]. This indicates that the prostaglandins may have effects to improve symptoms of incipient diabetic nephropathy by alleviating constriction of efferent glomerular arteriole, which is induced by angiotensin II.

Additionally, it has been indicated that the increased production of thromboxane A₂ in kidneys may be another factor to aggravate the symptoms of diabetic nephropathy, due to inducing platelet aggregation in glomeruli [4, 5]. PGI₂ is mainly produced in vascular endothelial cells and has a very strong effect to inhibit platelet aggregation, which contradicts the effects of thromboxane A₂. Therefore, there may be a possibility that PGI₂ has effects to inhibit thromboxane A₂, and consequently protect aggravation of diabetic nephropathy.

We administered beraprost sodium, which is a stable derivative of PGI₂ for 24 months to patients who showed microalbuminuria due to incipient diabetic nephropathy,

and the effect of the drug on urinary albumin excretion, which is a marker of incipient nephropathy, was evaluated in this study.

Subjects and Methods

Twenty-seven outpatients (12 males and 15 females) who were diagnosed as having incipient diabetic nephropathy due to type 2 diabetes mellitus were enrolled as subjects for this study after obtaining informed consent. The incipient nephropathy was defined as patients whose urinary albumin excretion level was 30 mg/day or more and less than 300 mg/day calculated from 24-hour urine collection samples taken for the third consecutive day.

These patients were randomly, but not blindly, assigned to two groups, either control group (group C; n = 13) or beraprost sodium group (group B; n = 14).

As shown in table 1, there were no differences at the baseline in age, duration from the onset of the diabetes, control status of the disease, medication for the disease, complication rate of hypertension, antihypertensive medication and urinary albumin excretion levels between the two groups. Kidney biopsy was not performed in any of the cases; however, either simple retinopathy or proliferative retinopathy was revealed in all cases. All patients underwent ultrasonography for kidney evaluation; however, no abnormality such as hydronephrosis was found.

The duration of the study was 24 months, and 120 µg of beraprost sodium (Procylin®, Kaken Pharmacy Co. Ltd., Tokyo, Japan) was orally administered for 24 months in patients in group B. Beraprost sodium (IUPAC: sodium (±)-(1R*,2R*,3aS*,8bS*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(E)-(3S*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butylate) is an orally active and stable prostacyclin analogue, which produces vascular relaxation and inhibition of platelet adhesion/aggregation. The pharmacological action of beraprost sodium is considered due to the activation of adenylate cyclase through prostacyclin receptors on platelet and smooth muscle cell membrane, and consequent increase of intracellular cyclic adenosine monophosphate (cAMP) and suppression of Ca²⁺ inflow. No concomitant drugs such as antiplatelet, anticoagulant, thrombolytic agents or nonsteroidal anti-inflammatory drugs (NSAID) were used. It has previously been reported that the glucose control did not improve albuminuria in the period of microalbuminuria [6]; however, some authors inversely report the glucose control decreased albuminuria [7, 8]. Therefore, we maintained the dosages of oral hypoglycemic agent and insulin preparation constant during the study period to stabilize the glucose level of the subjects. As far as the diabetic diet (25–35 kcal/kg of an average body weight) is concerned, which had been adopted by patients before enrolment for this study, we tried to maintain the caloric intake of individual patient constant during the study period. For those who had hypertension, we advised them to restrict salt intake within 7 g/day. And in all cases, blood pressure had been controlled under the systolic pressure of 150 mm Hg and the diastolic pressure of 90 mm Hg using antihypertensive agent since 3 months before enrolment to this study. ACE-I were not administered for possible decrease of albuminuria in incipient diabetic nephropathy [9]. Antihypertensive drugs other than ACE-I were permitted to administer, however, as there are reports that albuminuria was decreased due to lowered blood pressure in incipient diabetic nephropathy [10, 11], the cases that

Table 1. Baseline characteristics

	Control group (n = 13)	Beraprost sodium group (n = 14)	p value between the two groups
Age, years	61.4 ± 8.6	57.3 ± 10.0	0.265
Duration from the onset of DM, years	15 ± 2	14 ± 3	0.317
HbA1c, %	8.3 ± 1.9	8.5 ± 1.6	0.733
Low caloric diet alone	3	0	0.056
Oral hypoglycemic drug	7	11	0.173
Insulin	3	3	0.918
Complication of hypertension (rate)	12 (92.3%)	10 (71.4%)	0.162
Salt restriction alone	1	0	0.29
Ca blocker	5	4	0.585
α1 blocker	0	1	0.326
β2 blocker	1	0	0.29
Ca blocker and α1 blocker	0	1	0.326
Ca blocker and β2 blocker	4	2	0.303
Ca blocker and α1 blocker and β2 blocker	1	2	0.585
Urinary albumin excretion, mg/day	108.9 ± 92.8	137.8 ± 98.8	0.441

Values are expressed as means ± SD.

Mann-Whitney U test was used to analyze age, duration of the diabetes mellitus, HbA1c, and urinary albumin
 χ^2 test was used for other variables.

required additional medication to control blood pressure or the cases that required reduction of the dosage of the antihypertensive drug due a decrease of the systolic pressure by 30 mm Hg or more were excluded from this study.

Urinary Albumin Excretion

Excretion of albumin in 24-hour urine collection samples was examined and compared by latex immunoagglutination assay every 6 months since the study was initiated. We asked all the patients in this study to avoid exercise on the day of the 24-hour urine collection, because exercise can affect urinary albumin excretion levels.

Renal Function

Serum creatinine level and 24-hour creatinine clearance level (Ccr) were examined and compared every 6 months. Glomerular filtration rate (GFR) evaluation with inulin clearance or isotope was not performed this time, because the complicated method for measurement of inulin clearance is not applicable to outpatients, and the isotope method is costly as well. Therefore, Ccr was adopted instead of GFR for evaluation of the renal function.

Diabetic Control

Hemoglobin A1c (HbA1c) was used as an index of glucose control level, and the levels were compared every 6 months since the study was initiated.

Protein Intake

The protein intake, which may affect the urinary albumin excretion [12–14], was evaluated and compared every 6 months. The protein intake was estimated using 24-hour urine collection samples with the method by Maroni and Mitch [15].

Lipid Metabolism

Because lipid metabolism is strongly involved in renal diseases [16–18] and abnormal lipid metabolism is readily recognized as complication in diabetes, the total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride were measured before and after the study and the levels were compared.

Statistical Analysis

For statistical analysis, software, Statistical Analysis System (SAS) was used. Each value represents mean ± SD, and the significant differences over time on urinary excretion of albumin, renal function, lipid metabolism, HbA1c and protein intake were evaluated using analysis of variance (ANOVA). Also, the Mann-Whitney U test was used for comparison of the baseline values between group C and group B including age, duration from the onset of the diabetes, HbA1c and urinary albumin excretion for the analysis of categorical variables on complication of hypertension, diabetic medication or antihypertensive medication, χ^2 test was used. $p < 0.05$ was considered significant.

Results

In group B, all of the 14 cases showed no side effects of Procylin and the entire 27 cases completed the 24-month trial.

Fig. 1. Change in urinary albumin excretion. ■ = Control group (n = 13); ● = beraprost sodium group (n = 14). * $p < 0.05$. Values are expressed as means $\pm$ SD.

Fig. 2. Change in serum creatinine. ■ = Control group (n = 13); ● = beraprost sodium group (n = 14). Values are expressed as means $\pm$ SD.

Urinary Excretion of Albumin

Urinary excretion of albumin in group C did not significantly fluctuate as shown in figure 1; however, there was a slight increasing tendency. In group B, on the other hand, the level before the administration of the drug was 137.8 ± 98.8 mg/day, and it was 100 ± 68.5 mg/day at month 6, 133.8 ± 95.3 mg/day at month 12, 76.8 ± 49.9

mg/day ($p < 0.05$) at month 18, and 87.1 ± 67.4 mg/day ($p < 0.05$) at month 24, respectively. After month 18, the levels decreased significantly. Difference was observed between the two groups after month 12; however, it was not significant ($p = 0.0673$ at month 24).

Fig. 3. Change in creatinine clearance. ■ = Control group (n = 13); ● = beraprost sodium group (n = 14). Values are expressed as means ± SD. * p = 0.04.

Fig. 4. Change in blood pressure. SBP = Systolic blood pressures; DBP = diastolic blood pressures; ■ = control group (n = 13); ● = beraprost sodium group (n = 14). Values are expressed as means ± SD.

Renal Function

As shown in figure 2, the baseline serum creatinine level was 0.9 ± 0.3 mg/dl in group C and it was 0.9 ± 0.4 mg/dl at month 24 ($p = 0.45$), and in group B, pre-administration level of 0.9 ± 0.3 mg/dl did not significantly fluctuate and it was 1.0 ± 0.5 mg/dl at month 24. As for Ccr in figure 3, it increased from 86.3 ± 42.6 to $98.4 \pm$

33.7 ml/min at month 24 in group C; however, the difference was not significant ($p = 0.07$). In group B, it fluctuated from 81.8 ± 22.1 to 74.9 ± 22.4 ml/min at month 24; however, the fluctuation was not significant ($p = 0.22$). At months 12 and 18, the levels of Ccr in group B were lower than those of group C; however, no significant differences were observed. At month 24, the level in group B

Fig. 5. Change in hemoglobin A1c. ■ = Control group (n = 13); ● = beraprost sodium group (n = 14). *p < 0.05. Values are expressed as means ± SD.

Fig. 6. Change in protein intake. ■ = Control group (n = 13); ● = beraprost sodium group (n = 14). Values are expressed as means ± SD.

was significantly low compared with that of group C (p = 0.04).

Blood Pressure

In all cases, no additional antihypertensive medication was adopted. No significant fluctuation over time was observed in both groups regarding systolic or diastolic

pressures. Therefore, it was considered that blood pressure which could be a possible factor on urinary excretion of albumin, remained stable during this study period, and it was indicated that there was no influence of blood pressure on the levels of albumin (fig. 4).

Table 2. Lipid

	Control group (n = 13)			Beraprost sodium group (n = 14)		
	pre	post	p	pre	post	p
Total cholesterol, mg/dl	208.9 ± 44.6	213.6 ± 45.2	0.41	202.0 ± 35.1	207.2 ± 39.5	0.50
HDL-cholesterol, mg/dl	42.0 ± 9.6	40.6 ± 10.0	0.54	39.2 ± 12.2	38.1 ± 10.4	0.58
LDL-cholesterol, mg/dl	131.3 ± 36.0	136.6 ± 36.6	0.19	112.9 ± 35.5	119.2 ± 27.4	0.37
Triglyceride, mg/dl	192.4 ± 96.1	179.4 ± 99.2	0.33	208.0 ± 102.2	242.0 ± 193.9	0.46

Values are expressed as means ± SD.

Diabetic Control

The dosages of oral hypoglycemic agent and insulin preparation were maintained constant during the study period to stabilize the glucose level in all cases. As shown in figure 5, HbA1c did not show any significant change in group C. In group B, the pre-administration level of $8.5 \pm 1.6\%$ significantly decreased to $7.7 \pm 1.0\%$ at month 6 ($p < 0.05$); however, no significant fluctuation was observed after month 12 until month 24. As there was no decrease in urinary albumin level at month 6, it was considered that this significant fall of HbA1c did not contribute to the albumin levels. These results indicate that the diabetic control, a factor which could affect the urinary albumin levels, did not contribute to the urinary albumin levels in this study.

Protein Intake

The protein intake in both groups did not change significantly over time as shown in figure 6. Therefore, it was considered that the protein intake, a factor that could affect urinary albumin levels, did not contribute to the albumin levels this time, remaining constant during the study period.

Lipid

No significant fluctuation was observed in lipid parameters during the study period (table 2).

Discussion

In this study, we found that a PGI₂ preparation, beraprost sodium, reversibly decreased urinary albumin excretion levels. Under the condition that major three factors, e.g. blood pressure, protein intake and serum glucose level, are constant, which may contribute to urinary albu-

min levels, that is, independent to these three factors, the PGI₂ preparation, beraprost sodium, significantly decreased urinary albumin excretion levels starting from month 18 of the study period. The patients were randomized but not blindly; however, we doubt that this affected the results, because we focused on laboratory tests, but not symptoms or physical findings except for blood pressures.

In diabetic nephropathy, growth of mesangial cells is recognized in early stage, and PDGF has been said to contribute to the phenomenon [19]. It has been shown experimentally that the growth of mesangial cells was induced by PDGF, and the growth of the cells cultured in medium with high glucose concentration was inhibited by neutralizing antibody of PDGF and resulted in inhibition of collagen production in the cells [1]. It has also been shown that the beraprost sodium inhibited PDGF-induced growth of cultured vascular smooth muscle cells [20], and the mesangial cells which are similar in character to vascular smooth muscle cells may have been inhibited to proliferate, and consequently improved the symptoms of incipient diabetic nephropathy reversibly, according to our study this time.

Furthermore, it was shown experimentally that prostaglandins alleviated angiotensin II-induced constriction of efferent glomerular arteriole in vitro [3]. In diabetic nephropathy in rats, it has been reported that cicaprost, which is a PGI₂ analog, decreased urinary albumin levels at the same level as ACE-I, and alleviated diabetic renal injury by reducing the number of sclerotic glomeruli histologically [21]. The study suggested that PGI₂ might have reduced angiotensin II-induced constriction of mesangial cells and lowered intraglomerular pressure and resulted in decrease of urinary albumin levels. It was reported that urinary albumin excretion was reduced by beraprost sodium in streptozotocin-induced diabetic rats [22]. Since Ccr

was simultaneously decreased by beraprost sodium, the authors postulated that beraprost sodium might improve glomerular hyperfiltration due to its vasodilating effects.

The results of the present long-term study also indicated that differences in Ccr levels began to be observed in both groups beginning from month 12, which were not significant, but the differences became statistically significant at month 24. According to the studies above, we have a hypothesis that PGI₂ may have reduced GFR (Ccr) by reducing intraglomerular pressure due to dilation of glomerular efferent arteriole or mesangial cells, resulting in decrease of urinary albumin levels, although reductions in GFR do not necessarily mean a reduction in intraglomerular pressure. However, the mechanism that PGI₂ inhibits angiotensin II-mediated hyperfiltration to decrease urinary albumin levels may not be attributed markedly in the present study. The reason is that it was after month 12 when urinary albumin excretion level began to fall and after month 24 when the differences were observed in Ccr levels between the two groups, and when compared with those of ACE-I it was considered that the onset of effects of PGI₂ was very slow. In any event, since decreased levels of PGI₂ in diabetes have been recognized in human [23], PGI₂ medication seems to be reasonable.

The Ccr levels of 86.3 ± 42.6 ml/min in group C and 81.8 ± 22.1 ml/min in group B at baseline were not indicative of glomerular hyperfiltration in this study. This finding is consistent with the results of a study which reports incipient nephropathy in non-insulin-dependent diabetes mellitus (NIDDM) may not necessarily show glo-

merular hyperfiltration as the insulin-dependent diabetes mellitus (IDDM) does [24]. There seems to be no study so far which examined GFR in a time-dependent manner in incipient diabetic nephropathy; however, long-term studies on incipient nephropathy in NIDDM may indicate that GFR will increase time-dependently within the normal range.

We did not perform the platelet aggregation test this time; however, PGI₂ preparations may be able to inhibit thromboxane A₂ and inhibit platelet aggregation, and consequently may protect the diabetic nephropathy from being aggravated when viewed from long-range perspective. Also, it has been reported that the thromboxane stimulates mesangial cells to produce their matrix protein in diabetic rats [25]; therefore, beraprost sodium may be able to inhibit the above action to inhibit aggravation of the disease.

In conclusion, the PGI₂ preparation, beraprost sodium, decreased urinary albumin excretion levels after month 18 of the drug administration under the condition that three factors, e.g. blood pressure, protein intake and serum glucose levels, were stable. Beraprost sodium may have inhibited growth of mesangial cells induced by PDGF, or may have alleviated angiotensin II-induced constriction of glomerular efferent arteriole or mesangial cells to reduce intraglomerular pressure or inhibited the action of thromboxane A₂, and therefore, consequently platelet aggregation may have been inhibited. This is a great deal of potential mechanism to improve the symptoms of incipient diabetic nephropathy.

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