Clinical Effect of Addition of Beraprost Sodium to Pioglitazone Treatment on the Blood Glucose Levels in Patients with Type 2 Diabetes Mellitus

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Key words
- beraprost sodium
- pioglitazone
- HbA1c
- type 2 diabetes

Abstract

In recent years, the number of patients with type 2 diabetes mellitus caused by insulin resistance has continued to increase in Japan. Insulin resistance is considered to be closely related to the risk of cardiovascular diseases and atherosclerotic diseases, represented by arteriosclerosis obliterans (ASO). Therefore, improvement of insulin resistance is one of the important strategies in the treatment of type 2 diabetes mellitus. At present, α-glucosidase inhibitors, incretin-related drugs, and thiazolidinediones are among the most important oral hypoglycemic drugs used to improve insulin resistance. In this study, the effect of beraprost sodium, a prostaglandin I2 derivative, in the treatment of type 2 diabetes mellitus was investigated. In type 2 diabetic patients with ASO who were under treatment with pioglitazone, additional treatment with beraprost sodium exerted a significant synergistic effect in reducing the serum HbA1c levels as compared to treatment with pioglitazone alone. This result indicates that concomitant administration of pioglitazone and beraprost sodium may be useful in the treatment of diabetes mellitus.

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Introduction

In recent years, the number of patients with type 2 diabetes mellitus has continued to increase in Japan due to the westernization of lifestyles. The number of diabetic patients in Japan was estimated to be approximately 22 100 000 in March 2010, according to "the National Health and Nutrition Survey in Japan, 2007" published by the Ministry of Health, Labor and Welfare. Impaired insulin secretion and insulin resistance are the most important pathophysiological abnormalities underlying the development of type 2 diabetes mellitus. Environmental factors, such as obesity, bulimia and lack of exercise are strongly involved in the development of insulin resistance, which might indicate why the prevalence of type 2 diabetes mellitus caused by insulin resistance is increasing. In addition, insulin resistance is considered to be closely related to the risk of cardiovascular diseases and atherosclerotic diseases, represented by arteriosclerosis obliterans (ASO) [1]. Therefore, improvement of insulin resistance is one of the important strategies in the treatment of type 2 diabetes mellitus. At present, biguanides and thiazolidinediones are among the most important oral hypoglycemic drugs used to improve insulin resistance. In Japan, biguanides are not often used, and mainly pioglitazone, a thiazolidinedione, is used in the treatment of insulin resistance.

On the other hand, beraprost sodium, which is a derivative of a biological molecule, namely, prostaglandin I_2, has been shown to have strong antiplatelet and vasodilatory effects and is used as a therapeutic agent against ASO, an atherosclerotic disease, and pulmonary hypertension. Recently, it was reported that beraprost sodium reduces serum glucose, insulin, triglyceride, and total cholesterol levels in obese rats [2], and improves glucose tolerance through PPARγ mRNA expression in high-fat-fed obese mice [3]. In type 2 diabetic patients, beraprost sodium reduces serum TNF-α level [4]. Kubota et al. showed in a study of a mouse model of obesity and diabetes, that beraprost sodium activates endothelial nitric oxide synthase (eNOS) and thereby improves decreased glucose uptake associated with obesity in the muscle via the vasodilatory effect of eNOS [5].

In addition, it was reported that pioglitazone induces COX-2 mRNA expression and consequently

increases prostacyclin production in rats [6]. Although these drugs have partial similar effect on diabetic model animals, the effects of beraprost sodium on glycemic and lipid condition in pioglitazone-treated or non-treated diabetics with ASO have not been documented well.

In the present study, we retrospectively investigated the clinical effect of beraprost sodium on the serum glycemic and lipid condition in type 2 diabetic patients with ASO.

Subjects and Methods

Study population

The subjects were 28 type 2 diabetic patients, consisting of 21 men and 7 women with ASO who attended the Akishima Clinic (Nagoya Japan), and who, in addition to their antidiabetic treatment, additionally received 120 µg/day of beraprost sodium (Procylin® tablet 20, Kaken Pharmaceutical, Tokyo, Japan) for the treatment of ASO. The subjects were divided into a group receiving 30 mg/day of pioglitazone for the treatment of diabetes mellitus (pioglitazone-treated group) and a group receiving other oral blood glucose-lowering agents (non-pioglitazone-treated group), and the changes in the body weight, body mass index (BMI), fasting serum HbA1c levels, and serum lipid levels before and after the addition of beraprost sodium to the antidiabetic treatment were analyzed. The mean duration of additional treatment with beraprost was 6.4 ± 2.6 months. The treatment backgrounds, including the diet and exercise therapies, were similar between the 2 groups, except for the use of pioglitazone, and patients using insulin were excluded. ASO was diagnosed based on a history of subjective symptoms, such as coldness and numbness of the lower extremities, and palpation.

All patients attending the clinic gave their written consent at the first examination for data disclosure in the post-marketing surveillance, etc.

Background parameters of patients

The background characteristics of the patients participating in the study are shown in **Table 1**. The body weight, BMI and laboratory test values before the addition of beraprost sodium to the antidiabetic treatment were compared between the pioglitazone-treated group and non-pioglitazone-treated group. The serum TG levels were significantly lower in the pioglitazone-treated group, and the values of all the other parameters examined were equivalent between the 2 groups. The serum HbA1c level (NGSP) was controlled to some extent by the oral blood glucose-lowering agents, and was 6.9 ± 1.7 % in the non-pioglitazone-treated group and 6.7 ± 0.5 % in the pioglitazone-treated group.

Body weight measurements and blood analyses

Body weight was measured with the electronic load cell scales (TANITA, Tokyo, Japan).

Serum lipids were determined by Auto Dry Chemistry Analyzer (Arkray, Kyoto, Japan). Blood glucose was determined by standard enzymatic method (Sanwa Kagaku Kenkyusho, Nagoya, Japan). HbA1c was determined by HPLC method (Arkray).

Statistical analysis

The results were calculated as the mean ± SD (or median, only for TG level). Comparison of the parameters before and after the addition of beraprost sodium and between the pioglitazone- and non-pioglitazone-treated groups were performed by 2-sided, paired Student's t-test, and the serum TG levels were log-transformed for comparisons. Statistical significance was set at $p < 0.05$.

Results

Effects of addition of beraprost sodium

Fig. 1 shows the body weight, BMI, blood glucose, and serum lipid conditions in subjects before and after treatment of beraprost sodium. Significant reductions of the body weight and BMI were observed after additional treatment with beraprost sodium ($p < 0.01$, respectively) in the non-pioglitazone-treated group. On the other hand, these values did not change significantly in the pioglitazone-treated group.

Regarding the blood glucose, the values did not change significantly in the pioglitazone-treated group and in the non-pioglitazone-treated group.

Serum HbA1c (NGSP) showed no significant change in the non-pioglitazone-treated group, but decreased significantly from 6.7 ± 0.5 to 6.2 ± 0.4 % ($p < 0.01$) after additional treatment with beraprost sodium in the pioglitazone-treated group.

Among serum lipids, the non-pioglitazone-treated group showed significant reduction of the serum total cholesterol (TC) and TG levels (TC: $p < 0.01$; TG: $p < 0.05$), however, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) showed no significant change. Whereas no significant changes of these serum lipid levels were observed in the pioglitazone-treated group.

Safety

No adverse effects likely to be associated with beraprost sodium treatment or hypoglycemia were observed in any of the patients.

	Non-pioglitazone-treated group	Pioglitazone-treated group
patient number (male/female)	18 (13/5)	10 (8/2)
age (years)	59.6 ± 13.8	62.5 ± 11.9
body weight (kg)	67.3 ± 17.3	69.0 ± 11.7
body mass index (kg/m^2)	24.8 ± 5.3	24.8 ± 5.8
blood glucose (mg/dL)	133 ± 46	135 ± 41
HbA1c (NGSP, %)	6.9 ± 1.7	6.7 ± 0.5
TC (mg/dL)	183 ± 49	160 ± 27
HDL-C (mg/dL)	49 ± 14	56 ± 7
LDL-C (mg/dL)	107 ± 41	90 ± 30
TG (median, mg/dL)	161	88

Table 1 Patient background before the addition of beraprost sodium to the oral antidiabetic treatment regimen. Data are expressed as mean ± SD. TC, serum total cholesterol; HDL-C, serum high-density lipoprotein cholesterol; LDL-C, serum low-density lipoprotein cholesterol; TG, serum triglyceride.

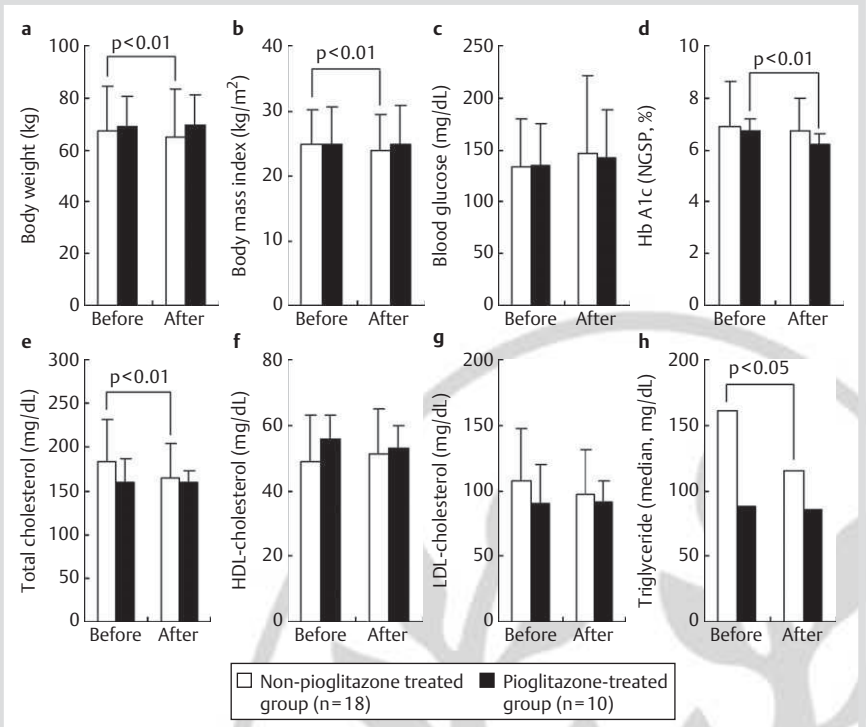

Fig. 1 Clinical effect of beraprost sodium on the body weight **a**, body mass index **b**, blood glucose **c**, serum HbA1c (NGSP, **d**), serum total cholesterol **e**, serum HDL-cholesterol **f**, serum LDL-cholesterol **g**, and serum triglyceride **h**. "Before": before addition of beraprost sodium, "After": 6.4 months, on average, after addition of beraprost sodium.

Discussion

The clinical effect of additional treatment with beraprost sodium, a drug used for the treatment of ASO, on the blood glucose levels was investigated in type 2 diabetic patients with ASO. The results revealed that additional treatment with beraprost sodium exerted lowering effect in the serum HbA1c levels in the pioglitazone-treated group. Although the reason remains unclear, the HbA1c reduction might be related to synergistic effect of improvement of the insulin resistance by the vasodilatory effect of beraprost sodium.

On the other hand, no improvement of the serum HbA1c levels with additional beraprost sodium treatment was observed in the non-pioglitazone-treated group. This could be because the serum HbA1c levels (NGSP) may have already been controlled to some extent (6.9%, on average) before the start of additional treatment with beraprost sodium. Actually, in the present study also, the serum HbA1c levels were reduced by approximately 1.0% from 8.8±1.8 to 7.8±1.3% in the non-pioglitazone-treated group with HbA1c levels (NGSP) of 6.9% or higher, although the difference was not significant because of the small number of cases. Sato et al. also reported that beraprost sodium tended to lower HbA1c level dose-dependently in obese Zucker rats [2]. Therefore, it is possible that additional treatment with beraprost sodium may be especially effective in further reducing the blood glucose levels in type 2 diabetic patients showing poor glycemic control.

While the HbA1c levels decreased, none of the patients developed hypoglycemia. Post-marketing surveillance of beraprost sodium has revealed no event of hypoglycemia among more than 7000 treated cases, suggesting that this drug can be used safely. Kubota et al. reported that although beraprost sodium improved insulin delivery through telangiectasia and thereby improved glucose uptake in the skeletal muscle, it did not completely improve glucose uptake impairment in the skeletal muscle itself [5]. It is speculated that such a characteristic effect of beraprost sodium is one of the reasons for the non-occurrence of hypoglycemia as an adverse effect.

The body weight and BMI decreased significantly in the non-pioglitazone-treated group, but did not change in the pioglitazone-treated group. The diet and exercise therapies were conducted in both groups, and any decrease in body weight was considered to be counterbalanced by the weight-gain effect of pioglitazone. It is reported that beraprost sodium (0.2–0.3 mg/kg/day) does not affect body weight in obese rats [2,3]. Thus, the reduction of body weight may not be attributed to beraprost sodium. While it was reported that low-dose pioglitazone (7.5 mg/day) improved glycemic control without increasing significant body weight [7,8], in the present study, the subjects received 30 mg/day of pioglitazone. Therefore, reduction of the pioglitazone dose may improve the blood glucose levels without such adverse effects as weight gain.

Among the serum lipids, the serum TC and TG levels decreased significantly only in the non-pioglitazone-treated group. This result was consistent with previous reports that beraprost sodium has a serum lipid-improving effect in rats [2,9]. Absence of changes in the serum lipid levels in the pioglitazone-treated group may possibly be attributable to the lower serum lipid levels before the additional treatment with beraprost sodium in the non-pioglitazone-treated group.

Although the number of cases in the present study was probably insufficient to verify the clinical effects of beraprost sodium, the additional effects of beraprost sodium in pioglitazone-treated diabetics with ASO have not been reported so far. The results suggest that addition of beraprost sodium to the antidiabetic treatment regimen may be a useful novel strategy in the treatment of type 2 diabetes mellitus. In the future, it would be desirable to conduct prospective studies with a larger number of cases for accumulating valid clinical data.

Conflict of interest: The authors report no conflicts of interest.

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References

1 *Rajwani A*, *Cubbon RM*, *Wheatcroft SB.* Cell-specific insulin resistance: implications for atherosclerosis. Diabetes Metab Res Rev 2012; 28: 627–634
2 *Sato N*, *Kaneko M*, *Tamura M et al.* The prostacyclin analog beraprost sodium ameliorates characteristics of metabolic syndrome in obese Zucker (fatty) rats. Diabetes 2010; 59: 1092–1100
3 *Inoue E*, *Ichiki T*, *Takeda K et al.* Beraprost sodium, a stable prostacyclin analogue, improves insulin resistance in high-fat diet-induced obese mice. J Endocrinol 2012; 213: 285–291
4 *Fujiwara K*, *Nagasaka A*, *Nagata M et al.* A stable prostacyclin analogue reduces high serum TNF-α levels in diabetic patients. Exp Clin Endocrinol Diabetes 2004; 112: 390–394
5 *Kubota T*, *Kubota N*, *Kumagai H et al.* Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. Cell Metab 2011; 13: 294–307
6 *Hernanz R*, *Martín Á*, *Péres-Girón JV et al.* Pioglitazone treatment increases COX-2-derived prostacyclin production and reduces oxidative stress in hypertensive rats: role in vascular function. Br J Pharmacol 2012; 166: 1303–1319
7 *Majima T*, *Komatsu Y*, *Doi K et al.* Safety and efficacy of low-dose pioglitazone (7.5 mg/day) vs. standard-dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes mellitus. Endocr J 2006; 53: 325–330
8 *Aso Y*, *Hara K*, *Ozeki N et al.* Low-dose pioglitazone increases serum high molecular weight adiponectin and improves glycemic control in Japanese patients with poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2009; 85: 147–152
9 *Chatzipanteli K*, *Rudolph S*, *Axelrod L.* Coordinate control of lipolysis by prostaglandin E2 and prostacyclin in rat adipose tissue. Diabetes 1992; 41: 927–935