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Pioglitazone produces rapid and persistent reduction of vascular inflammation in patients with hypertension and type 2 diabetes mellitus who are receiving angiotensin II receptor blockers

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Abstract

Inhibition of the renin-angiotensin system reportedly exerts potent antiatherogenic effects by reducing vascular inflammation. We tested the hypothesis that pioglitazone, a peroxisome proliferator–activated receptor γ agonist, further reduces vascular inflammation in patients receiving angiotensin II receptor blockers. Patients with hypertension who had developed type 2 diabetes mellitus were randomly assigned to receive either pioglitazone (15 mg/d, n = 20) or voglibose, an α-glucosidase inhibitor (0.6 mg/d, n = 19) for 6 months, and changes in their serum concentrations of C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) were monitored. Pioglitazone, but not voglibose, reduced CRP levels within 1 month ($-51\% \pm 7\%$, mean ± SEM; $P < .001$). C-reactive protein levels were decreased after 6 months of treatment with either pioglitazone or voglibose, with the former being more effective ($-57\% \pm 8\%$ vs $-9\% \pm 18\%$; $P < .05$). The levels of ICAM-1 and VCAM-1 were significantly reduced after 1 month of pioglitazone therapy ($-9\% \pm 3\%$ and $-8\% \pm 3\%$, respectively; both $P < .05$), with the beneficial effects persisting throughout the study period. In contrast, the levels of ICAM-1 and VCAM-1 were not altered during the study period in patients on voglibose. There was no correlation between the reduction of hemoglobin A_{1c} and that of CRP, ICAM-1, or VCAM-1. These results suggest that augmentation with pioglitazone further reduces vascular inflammation in patients with hypertension and diabetes who are receiving angiotensin II receptor blockers. This may contribute to the reduction of cardiovascular events in this at-risk population.

1. Introduction

Patients with essential hypertension are likely to develop diabetes [1,2], and individuals with hypertension and diabetes mellitus are at a high risk of atherothrombotic disease [3-5]. Such patients benefit more from the hypertension than the diabetes being treated aggressively [6]. Thiazide diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers are all reported to be beneficial in reducing cardiovascular diseases in patients with hypertension and diabetes [7], but treatment with angiotensin-converting enzyme inhibitors or ARBs would be the most attractive because the renin-angiotensin system is crucially involved in the process of atherosclerosis [8,9]. Indeed, atherosclerosis is an inflammatory disease of the vascular wall [10,11], and inhibition of the renin-angiotensin system by ARBs reportedly exerts potent anti-inflammatory effects [12,13].

Pioglitazone, a thiazolidinedione, is a peroxisome proliferator–activated receptor γ (PPAR-γ) agonist that enhances the action of insulin mainly by promoting glucose utilization in peripheral tissues and suppressing gluconeogenesis in the liver [14]. Thiazolidinediones can improve hyperglycemia and hyperinsulinemia and are currently used to manage type 2 diabetes mellitus [15,16]. Besides their beneficial effects on insulin sensitivity, there is accumulating evidence that thiazolidinediones have antiatherogenic properties [14,16-19]. PPAR-γ regulates the recruitment of monocytes to endothelial cells [20], inflammatory responses in macrophages [21,22], and the proliferation and migration

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Table 1
Baseline characteristics of patients and effects of pioglitazone and voglibose on clinical characteristics

Variable	Baseline		6 Months	
	Pioglitazone	Voglibose	Pioglitazone	Voglibose
No. of patients	20	19	20	19
Age (y)	67.8 ± 2.0	68.2 ± 1.7		
Sex (M/F), n	11/9	12/7		
BMI (kg/m^2)	24.7 ± 0.3	24.2 ± 0.6	24.8 ± 0.3	23.8 ± 0.5
SBP (mm Hg)	135.0 ± 3.0	134.7 ± 3.8	136.3 ± 2.4	136.0 ± 3.5
DBP (mm Hg)	77.7 ± 2.5	76.4 ± 1.6	76.6 ± 1.7	76.6 ± 2.2
TC (mmol/L)	5.99 ± 0.12	5.93 ± 0.15	6.06 ± 0.18	5.57 ± 0.20
TG (mmol/L)	2.79 ± 0.27	2.53 ± 0.20	1.99 ± 0.26**	1.81 ± 0.16**
HDL-C (mmol/L)	1.46 ± 0.09	1.35 ± 0.07	1.52 ± 0.11[a]	1.11 ± 0.09
LDL-C (mmol/L)	3.38 ± 0.13	3.45 ± 0.17	3.51 ± 0.18	3.55 ± 0.21
FPI (μU/mL)	10.0 ±1.1	9.8 ±1.1	6.5 ± 0.7**	8.7 ±1.0
FPG (mmol/L)	7.9 ± 0.4	7.7 ± 0.3	6.9 ± 0.3*	6.8 ± 0.2**
2-h PG (mmol/L)	15.6 ± 0.9	16.0 ± 0.4	12.6 ± 0.8**	12.1 ± 0.8***
HbA_{1c} (%)	7.0 ± 0.3	6.9 ± 0.2	6.2 ± 0.2*	6.2 ± 0.1***
HOMA-IR	3.59 ± 0.52	3.35 ± 0.41	2.01 ± 0.26**	2.71 ± 0.37
Medication				
Statin, n	7	5		
Fibrate, n	2	2		
Aspirin, n	2	2		

Data are mean ± SEM values except where indicated. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; FPI, fasting plasma insulin; 2-h PG, glucose levels 2 hours after a 75-g oral glucose tolerance test.

[a] $P < .01$ vs voglibose.

* $P < .05$.

** $P < .01$.

*** $P < .001$ vs baseline.

of vascular smooth muscle cells [21,23]. Moreover, in human clinical studies, pioglitazone reduces the level of C-reactive protein (CRP), a marker of systemic inflammation [24,25]. This last finding is of clinical interest because several prospective studies have demonstrated a direct association between CRP levels and the risks of developing cardiovascular disease [26,27]. Indeed, pioglitazone reduces the carotid intima-media wall thickness [28] and the composite of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes mellitus [29]. However, it is not clear whether pioglitazone exerts additional anti-inflammatory effects in subjects receiving inhibitors of the renin-angiotensin system. Thus, the present study was designed to investigate whether pioglitazone reduces vascular inflammation in patients with hypertension and type 2 diabetes mellitus who are receiving treatment with ARBs. α-Glucosidase inhibitors are widely used for treating diabetic patients [30] and reduce the risk of cardiovascular disease [31,32]. We used an α-glucosidase inhibitor, voglibose, to actively control pioglitazone.

2. Subjects and methods

The present study was conducted according to the principles expressed in the Declaration of Helsinki. The

Table 2
Effects of pioglitazone and voglibose on inflammation and endothelial function

	Pioglitazone			Voglibose		
	Baseline	1 Month	6 Months	Baseline	1 Month	6 Months
CRP (mg/dL)	0.17 ± 0.09	0.05 ± 0.02***	0.05 ± 0.02***	0.14 ± 0.09	0.10 ± 0.04	0.08 ± 0.04*
CRP subgroup						
High[a]	0.31 ± 0.08	0.05 ± 0.03**	0.06 ± 0.05***	0.36 ± 0.13	0.24 ± 0.12	0.14 ± 0.06*
Low[b]	0.09 ± 0.04	0.05 ± 0.02**	0.04 ± 0.01**	0.07 ± 0.02	0.06 ± 0.01	0.06 ± 0.02
ICAM-1 (mg/L)	0.25 ± 0.04	0.22 ± 0.03**	0.20 ± 0.04**	0.24 ± 0.05	0.23 ± 0.05	0.21 ± 0.05
VCAM-1 (mg/L)	0.53 ± 0.09	0.46 ± 0.07**	0.41 ± 0.05***	0.47 ± 0.06	0.43 ± 0.06	0.50 ± 0.11

Data are median ± median absolute deviation values. Variables were evaluated by analysis of variance for repeated measures after logarithmic transformation followed by a Bonferroni post hoc test.

[a] Baseline CRP level higher than the median value.

[b] Other baseline CRP level.

* $P < .05$ vs baseline.

** $P < .01$.

*** $P < .0001$.

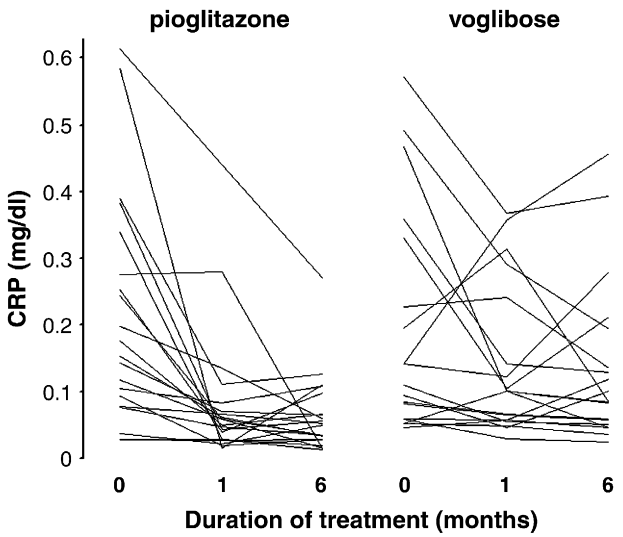

Fig. 1. Changes in the level of CRP in each patient after 1 and 6 months of treatment with pioglitazone or voglibose.

study protocol was approved by the ethics committee of Enshu General Hospital, Hamamatsu, Japan. All patients gave informed written consent to participate before the start of the study.

2.1. Subjects

Patients consistent with the following 3 criteria were eligible for inclusion in the study: (1) the presence of essential hypertension, (2) the recent development of type 2 diabetes mellitus, and (3) receiving monotherapy with ARBs for at least 6 months and not taking antidiabetic drugs, but on a diabetic diet. The diagnosis of essential hypertension was based on careful evaluation of clinical history, physical examinations, and laboratory and radiological investigations. Diabetes mellitus was diagnosed by using the 75-g oral glucose tolerance test. Exclusion criteria were current smoking habit, cardiovascular disease, valvular heart disease, congestive heart failure, severe arrhythmia, and pulmonary, hepatic, renal (serum creatinine >1.2 mg/dL), active inflammatory, and malignant diseases. Subjects under treatment with insulin were also excluded from enrollment. None of the patients were receiving hormone replacement therapy.

2.2. Procedures

A total of 56 outpatients with essential hypertension were screened at Enshu General Hospital between January 2004 and March 2005, of which the 39 who were deemed eligible for the present study were randomly assigned to receive either pioglitazone (15 mg/d, n = 20) or voglibose (0.6 mg/d, n = 20) for 6 months. A computer-generated random number sequence was obtained and the sealed envelope method was used for randomization, which was not blocked or stratified. Serum concentrations of CRP, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) were measured at baseline and after 1 and 6 months of treatment. At the end of the study, pioglitazone or voglibose was withdrawn and the 75-g oral glucose tolerance test was repeated.

2.3. Biochemical measurements

Blood and urine were sampled in the morning after overnight fasting. The blood samples were centrifuged at 1000*g* for 15 minutes, and the resulting supernatant was stored at −70°C until use. For plasma separation, each blood sample was immediately transferred to chilled siliconized glass tubes containing EDTA (1 mg/mL) and centrifuged at 4°C. Plasma samples were frozen and then stored at −70°C until used in assays for fasting plasma glucose (FPG) and immunoreactive insulin concentrations. Fasting plasma glucose, hemoglobin A_{1c} (HbA_{1c}), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured according to standard procedures. Immunoreactive insulin was measured by an enzyme immunoassay using a commercially available kit (Tosoh, Tokyo, Japan). Insulin resistance was quantified by using a homeostasis model assessment for insulin resistance (HOMA-IR) [33]. C-reactive protein was measured by using a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Marburg, Germany) [34]. Serum levels of soluble ICAM-1 and VCAM-1 were measured by an enzyme-linked immunosorbent assay technique (R&D Systems, Minneapolis, MN).

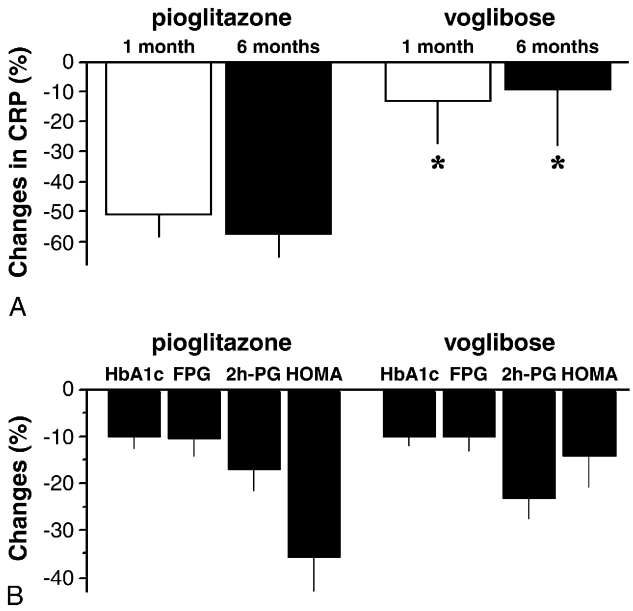

Fig. 2. Percentage changes in the CRP levels after 1 and 6 months of treatment with pioglitazone or voglibose relative to baseline (A) and percent changes in HbA_{1c} levels (B), glucose levels at fasting (FPG) and 2 hours after a 75-g oral glucose tolerance test (2h-PG), and HOMA-IR (HOMA) after 6 months of treatment with pioglitazone or voglibose relative to baseline. *$P < .05$ vs pioglitazone.

2.4. Statistical analysis

Except where otherwise stated, all data are expressed as mean ± SEM. Differences between 2 means of normal distributions were compared by unpaired Student t tests. Because the distributions of CRP, ICAM-1, and VCAM-1 levels were skewed rightward, the concentrations of these variables are expressed as median ± median absolute deviation values. Changes in these variables after the treatment were evaluated by analysis of variance for repeated measures after logarithmic transformation of these variables (which resulted in normal distributions). A Bonferroni post hoc test was used when significance was indicated. Univariate analyses were performed and stepwise multiple regression analysis was conducted to evaluate dependencies between variables. Yates corrected χ^2 test was used for comparisons between categorical data. $P < .05$ was considered statistically significant.

3. Results

A total of 39 patients with both hypertension and type 2 diabetes mellitus were randomized and subjected to analyses. Both treatments were well tolerated, and the follow-up was 100%. Table 1 lists the baseline demographic details of the 39 patients who were included in the intention-to-treat analysis. Their age was 68.0 ± 1.3 years, systolic/diastolic blood pressures were 134.9 ± 2.4/77.1 ± 1.5 mm Hg under treatment with ARBs, and HbA_{1c} level was 7.0% ± 0.2%. The baseline characteristics including CRP, ICAM-1, and VCAM-1 levels were not different in the 2 groups (Table 2).

The level of CRP was decreased after 1 month of treatment with pioglitazone but not with voglibose (Fig. 1 and Table 2). The CRP levels were lower after 6 months of treatment with either pioglitazone or voglibose, with the former being more effective (Figs. 1 and 2A, Table 2). Treatment with pioglitazone for 1 or 6 months reduced CRP levels in both patients with high and low baseline levels of CRP (Table 2). In contrast, voglibose reduced CRP levels only after 6 months of the treatment in patients with a high baseline level of CRP. The levels of ICAM-1 and VCAM-1 were significantly reduced after 1 month of pioglitazone therapy (−9% ± 3% and −8% ± 3%, respectively), with these beneficial effects persisting throughout the study period (−11% ± 3% and −17% ± 3% at 6 months, respectively; Table 2). In contrast, the levels of ICAM-1 and VCAM-1 were not altered during the study period in the patients who received voglibose. Hemoglobin A_{1c} levels and glucose levels at fasting and 2 hours after a 75-g oral glucose tolerance test were decreased to a similar extent in the 2 groups after 6 months of treatment (Table 1 and Fig. 2B). There was no correlation between the change in HbA_{1c} and that in CRP ($r = 0.101$, $P = .54$), ICAM-1, or VCAM-1 (data not shown). Similarly, changes in glucose levels and HOMA-IR were not correlated with those of CRP, ICAM-1, or VCAM-1 (data not shown). There was no correlation between the change in CRP and that in ICAM-1 or VCAM-1 (data not shown). Pioglitazone therapy tended to increase HDL-C levels ($P = .056$), and after 6 months of the treatments the level was higher in patients on pioglitazone than in those on voglibose (Table 1). The 2 antidiabetic drugs reduced the level of TGs to a similar extent.

Univariate analyses revealed that pioglitazone therapy ($r = 0.378$, $P < .05$) and body mass index (BMI) at baseline ($r = -0.334$, $P < .05$) were the predictors of a reduction in CRP levels, with only pioglitazone therapy remaining as a significant predictor of CRP reduction after adjusting for age, sex, BMI, blood pressure, HbA_{1c} levels, and HOMA-IR at baseline ($r = 0.422$, $P < .05$).

4. Discussion

Our study results demonstrated that pioglitazone rapidly reduced systemic inflammation in nonobese patients with hypertension and type 2 diabetes mellitus who were receiving ARBs. The reduction in CRP was accompanied by the reduction in the soluble adhesion molecules, indicating the antiatherogenic effects of the PPAR-γ agonist. The beneficial effect of pioglitazone was evident after 4 weeks of the treatment.

There is accumulating evidence that vascular inflammation is a central feature of atherosclerosis. The initial step of this process includes inflammatory activation of the endothelium in response to several risk factors such as hypertension and diabetes, which promote the expression of adhesion molecules on the surface of the endothelium and monocyte recruitment into the vascular wall [10,11]. Elevated concentrations of acute phase proteins or cell adhesion molecules are suggestive of the presence of inflammatory processes [26,27,35]. Based on this concept, increased CRP levels indicate an increased risk of cardiovascular events [26,27,35], and impaired endothelial function predicts the future development of coronary artery disease [36,37]. Thus, the circulating levels of inflammatory markers or adhesion molecules, such as CRP, ICAM-1, and VCAM-1 [35], represent attractive targets of antiatherosclerotic therapy, although it remains to be established that reducing the levels of these markers reduces the risk of atherothrombotic diseases. C-reactive protein levels are reportedly reduced by thiazolidinediones in diabetic patients [16,19,24,25,38] and by ARBs in hypertensive patients [12,13]. In the present study, pioglitazone further reduced the CRP levels within a month in patients receiving ARBs. In contrast, only a small (although significant) reduction in the CRP levels was observed after 6 months of treatment with voglibose, which may have been attributable to an improvement in glucose metabolism (FPG and 2-hour plasma glucose). Indeed, a meta-analysis has revealed that an α-glucosidase inhibitor, acarbose, reduces the risk of myocardial infarction [31]. The marker of inflammation decreased in response to voglibose only in the subgroup of

patients with a relatively high baseline level of CRP, which suggests that the beneficial effects of voglibose are greater in high-risk patients. However, it is obvious that the anti-inflammatory effects were much more pronounced in patients on pioglitazone than in those on voglibose. Thus, patients receiving inhibitors of the renin-angiotensin system would benefit further by augmentation with pioglitazone. This indicates that the PPAR-γ agonist exerts antiatherogenic effects, at least in part, by modifying pathways that are independent of the renin-angiotensin system. The present findings are consistent with the results of the PROspective pioglitAzone Clinical Trial In macroVascular Events study [29] in which pioglitazone effectively prevented macrovascular events.

In the present study, a reduction in CRP levels was observed in combination with the reduction in circulating levels of adhesion molecules (VCAM-1 and ICAM-1) in patients receiving pioglitazone. This is consistent with several sets of experimental data showing that PPAR-γ agonists reduce the expression of adhesion molecules in endothelial cells [17,20,35]. The suppression of the levels of soluble ICAM-1 and VCAM-1 by pioglitazone may indicate that the PPAR-γ agonist inhibits inflammatory activation of the endothelium, which is the initial step of atherosclerosis. Consistent with this speculation, treatment with pioglitazone is associated with a reduction of the intima-media wall thickness [28] and an improvement in the pulse wave velocity in patients with diabetes [24,28]. In contrast to changes in CRP levels, levels of the adhesion molecules were not altered in patients on voglibose, and hence it is possible that the improvement in systemic inflammation after antidiabetic therapy precedes the improvement of endothelial function. A high HDL-C concentration after pioglitazone therapy may be related to its anti-inflammatory effect. However, this may not be the fundamental factor responsible for the reduced vascular inflammation after pioglitazone treatment because pioglitazone did not significantly increase the HDL-C level and changes therein were not correlated with those in CRP, ICAM-1, or VCAM-1 (data not shown).

Another important finding from the present study is that short-term treatment with pioglitazone reduces inflammation and inflammatory activation of the endothelium in patients with hypertension and diabetes mellitus. Although the present study did not explicitly distinguish between the effects of pioglitazone on vascular inflammation and glucose metabolism, the results indicate that its anti-inflammatory effect is at least partially attributable to mechanisms that are independent of its antidiabetic effects. This confirms previous reports [24,25] and indicates that the antiatherogenic effect of pioglitazone is mediated primarily through a direct action on the vasculature. The present study is, however, subject to the following limitations: (1) the small number of patients included, (2) the markers investigated (ie, CRP, ICAM-1, and VCAM-1) are not established surrogate markers of atherothrombotic disease, and (3) a control group without any antidiabetic medication was not included. Moreover, the dose dependencies of the anti-inflammatory effects were not investigated in the present study, and higher doses of pioglitazone or voglibose might produce a greater reduction of vascular inflammation. However, it should be noted that pioglitazone at a dose that produced antidiabetic effects similar to those of voglibose resulted in much more potent anti-inflammatory effects. These limitations should be noted when interpreting present data.

In conclusion, although inhibition of the renin-angiotensin system has been reported to exert beneficial effects on vascular inflammation and endothelial function, augmentation with pioglitazone further reduces the inflammatory response. This may contribute to the reduction of cardiovascular events by pioglitazone in at-risk patients.

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