

Antiatherogenic Effect of Pioglitazone in Type 2 Diabetic Patients Irrespective of the Responsiveness to Its Antidiabetic Effect

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OBJECTIVE — Thiazolidinediones (TZDs), a class of insulin-sensitizing agents used clinically to treat type 2 diabetes, are also antiatherogenic. This study was designed to elucidate the relationship between the antiatherogenic and antidiabetic effects of pioglitazone, a TZD, in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 136 Japanese type 2 diabetic patients were included and divided into two groups: the pioglitazone-treated group (30 mg daily for 3 months) ($n = 70$) and the untreated control group ($n = 66$). The changes in glycolipid metabolism as well as plasma high-sensitivity C-reactive protein (CRP), leptin, adiponectin, and pulse wave velocity (PWV) were monitored to analyze the relationship between the antiatherogenic and antidiabetic effects of pioglitazone.

RESULTS — The pioglitazone treatment significantly reduced hyperglycemia, hyperinsulinemia, and HbA_{1c} levels and increased plasma adiponectin concentrations relative to the control group ($P < 0.01$). It also significantly decreased CRP and PWV ($P < 0.01$). The antiatherogenic effect was observed in both the nonresponders showing $<1\%$ of reduction in HbA_{1c} ($n = 30$) and responders showing $>1\%$ of reduction ($n = 40$). ANCOVA revealed that treatment with pioglitazone was associated with a low CRP and PWV, independent of the changes in parameters related to glucose metabolism.

CONCLUSIONS — This study represents the first demonstration of the antiatherogenic effect of pioglitazone in both nonresponders and responders with respect to its antidiabetic effect and suggests that pioglitazone can exert its antiatherogenic effect independently of its antidiabetic effect.

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Abbreviations: CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment for insulin resistance; IMT, intima-media wall thickness; IRI, immunoreactive insulin; PPAR- γ , peroxisome proliferator-activated receptor- γ ; PWV, pulse-wave velocity; SBP, systolic blood pressure; TZD, thiazolidinedione; VSMC, vascular smooth muscle cell;

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Type 2 diabetes contributes to the risk of developing atherosclerotic diseases such as coronary heart disease and stroke and coronary restenosis after angioplasty or stenting (1–4). Therefore, it is of clinical importance to evaluate and treat cardiovascular complications in type 2 diabetic patients beyond glycemic control.

Peroxisome proliferator-activated receptor- γ (PPAR- γ) is a member of the nuclear receptor superfamily that, when activated by insulin sensitizers of the thiazolidinedione (TZD) class, including troglitazone, pioglitazone, and rosiglitazone, regulates a host of target genes (5,6). In humans with and animal models of insulin resistance and type 2 diabetes, TZDs can improve hyperglycemia and hyperinsulinemia and are currently used to manage type 2 diabetes (7). PPAR- γ occurs abundantly in adipocytes where it regulates adipocyte differentiation (8), but it is also expressed in all major cell types participating in vascular injury, namely, endothelial cells, vascular smooth muscle cells (VSMCs), and macrophages (9,10). PPAR- γ regulates the recruitment of monocytes to endothelial cells (11), modulates the inflammatory response in monocytes/macrophages and VSMCs (12–14), and inhibits macrophage foam cell formation and VSMCs proliferation and migration (13–15). In experimental models of atherosclerosis, ligand-activated PPAR- γ prevents the progression of atherosclerotic lesions, with a concomitant reduction in macrophage accumulation in the atheromatous plaque (16–18). It is likely that the antiatherogenic effect of TZDs is mediated primarily through their direct action on the vasculature.

In human clinical studies that involve patients with type 2 diabetes, troglitazone and pioglitazone decreased the carotid arterial intima-media wall thickness (IMT) (19,20). Furthermore, it was recently reported that troglitazone reduced neointi-

Table 1—Baseline characteristics of patients treated with or without pioglitazone

Variables	Control	Pioglitazone
n	66	70
Sex (male/female)	32/34	32/38
Age (years)	59.3 ± 1.9	61.2 ± 1.3
BMI (kg/m ²)	23.0 ± 0.5	23.4 ± 0.4
SBP (mmHg)	146 ± 2	144 ± 2
DBP (mmHg)	82 ± 2	81 ± 2
FPG (mmol/l)	9.4 ± 0.3	9.6 ± 0.4
HbA _{1c} (%)	8.0 ± 0.2	8.1 ± 0.1
IRI (pmol/l)	55.9 ± 4.10	57.5 ± 3.96
HOMA-IR	3.30 ± 0.28	3.35 ± 0.29
Total cholesterol (mmol/l)	5.45 ± 0.16	5.46 ± 0.10
LDL cholesterol (mmol/l)	3.32 ± 0.11	3.30 ± 0.08
HDL cholesterol (mmol/l)	1.47 ± 0.10	1.44 ± 0.05
Triglycerides (mmol/l)	1.55 ± 0.04	1.56 ± 0.04
Adiponectin (μg/ml)	6.08 ± 0.42	6.03 ± 0.34
Leptin (ng/ml)	6.56 ± 0.45	6.52 ± 0.50
Treatment of diabetes (n)		
Diet alone	28	28
Diet + sulfonylureas	38	42
Diet + metformin	0	0
Use of antihypertensive medications (n)		
ACE inhibitors or angiotensin II receptor antagonists	0	0
Other	22	27
Use of lipid-lowering medications (n)		
Statins	19	13
Fibrates	3	1
Other	3	1

Data are means ± SEM. All group differences are nonsignificant.

mal tissue proliferation after coronary implantation in patients with type 2 diabetes (21,22). These observations indicate that TZDs may be therapeutically used as antiatherogenic as well as antidiabetic agents. Metabolic changes could contribute to the reduction in neointimal formation, although direct effects of troglitazone on the vasculature are likely to play a role in humans as well. However, whether TZDs can exert their antiatherogenic effect independent of their antidiabetic effect has never been addressed in humans.

It has been recognized that some type 2 diabetic patients respond to TZDs with the improvement of hyperglycemia and hyperinsulinemia (termed responders), whereas others do not (termed nonresponders) (23,24). Taking advantage of such differences, we studied the relationship between the antiatherogenic and antidiabetic effects of TZDs. Here we show that pioglitazone effectively reduces plasma high-sensitivity C-reactive protein (CRP) (25,26) levels, a marker of inflam-

mation, and pulse-wave velocity (PWV) (27,28), which is a direct parameter of arterial distensibility, in both nonresponders and responders to its antidiabetic effect.

This study is the first to provide evidence that pioglitazone can exert its antiatherogenic effect, irrespective of the responsiveness to its antidiabetic effect, thereby suggesting that the antiatherogenic effect of pioglitazone is mediated primarily via mechanisms distinct from its antidiabetic effect.

RESEARCH DESIGN AND METHODS

Subjects

A total of 136 Japanese patients with type 2 diabetes (64 men and 72 women, mean age 59.9 ± 1.4 years) participated in this study (Table 1). In our outpatient clinics during a specified period, we recruited type 2 diabetic patients who had stable and relatively high blood glucose and HbA_{1c} levels (HbA_{1c} 7.0–9.0%). We as-

signed the patients to the pioglitazone-treated and untreated groups one after the other. The patients were divided into the pioglitazone-treated group and the untreated control group. In the pioglitazone-treated group (n = 70), pioglitazone (30 mg daily) was administered for 3 months. Before the study, the 42 patients in the treatment group and 38 in the control group had been treated with sulfonylureas, whereas 28 and 28 patients, respectively, had been treated only with diet. Sulfonylureas were continued at fixed dosages throughout this study. None of patients in the treatment group and the control group had been treated with metformin. In this study, the pioglitazone-treated patients were divided into two groups according to their responsiveness to the treatment; the responders were those showing >1% of reduction in HbA_{1c} 3 months after the treatment, and the nonresponders were those showing <1% of HbA_{1c} reduction. This is based on the criteria of responders who showed a marked clinical response to the TZD and nonresponders who showed no response to it as demonstrated by Suter et al. (24). All patients were instructed to maintain the same level of energy intake and physical activity throughout this study. Patients treated with ACE inhibitors or angiotensin II receptor antagonists were excluded. Other antihypertensive medications were used in 17 patients in the treatment group and in 12 patients in the control group. Lipid-lowering medications, such as statins and fibrates were also used in the same proportion of patients in both groups. None of the patients of this study received hormone replacement therapy. This study was conducted after the study protocol was approved by the Ethical Committee on Human Research of Kyoto National Hospital and Saiseikai Noe Hospital and with the patients' informed consent.

Blood sampling, plasma separation, and biochemistry and hormonal assays

Blood was sampled at 0700 from the antecubital vein with the patient in the recumbent position after an overnight fast. 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 stored at –70°C until the assays for adiponectin and leptin

concentrations. Fasting plasma glucose (FPG), HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides levels were measured according to the standard procedures. Plasma insulin concentrations (immunoreactive insulin [IRI]) were measured by enzyme immunoassay using a commercially available kit (Tosoh, Tokyo, Japan). The insulin resistance index was assessed by homeostasis model assessment for insulin resistance (HOMA-IR) (29). Plasma levels of CRP were measured by the latex-enhanced assay using particle-enhanced technology performed on the Behring BN nephelometer (Dade Behring, Newark, DE) (30). Plasma concentrations of adiponectin and leptin were determined using the respective radioimmunoassay kits (Linco Research, St. Charles, MO), according to recommendations provided by the manufactures (31).

Measurements of blood pressure and PWV

Systolic and diastolic blood pressures (SBP and DBP) were measured twice with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan) with the patient in the sitting position after rest for at least 5 min.

A newly developed device that allows an automated multiple pulse wave measurement, ABI-form (model BP-203RPE, Nippon Colin) was used to measure PWV. This produced noninvasively four different parts PWVs in the body. PWV was measured before and 3 months after the pioglitazone treatment. In this study, PWV was calculated as the mean of left brachial-ankle PWV and that of right brachial-ankle PWV.

Statistical analysis

Data are presented as the mean \pm SEM, and $P < 0.05$ was considered statistically significant. Two-tailed Student's *t* test was used for baseline comparison between the two groups and comparison of differences between means within each group before and after the treatment. Differences among the nonresponders, responders, and control group were assessed with two-way repeated measures ANOVA with Fisher's protected least significant difference post hoc test. The pioglitazone treatment differences for Δ CRP, Δ adiponectin, and Δ PWV as dependent variables were assessed using ANCOVA models that include the following covari-

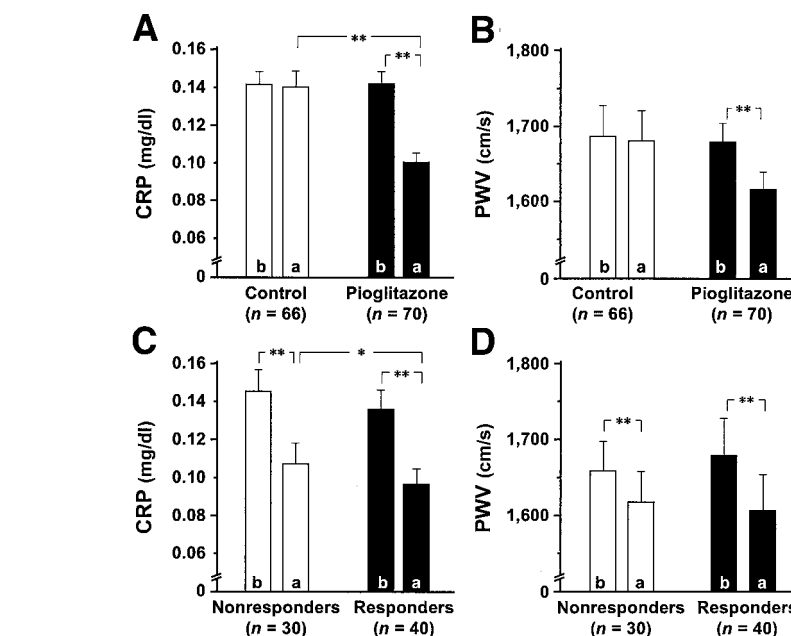


Figure 1—A and B: Plasma CRP levels and PWV in the control and pioglitazone-treated groups before and at the end of this study. Each column and bar represents the mean \pm SEM before (B) and after 3 months (A). ** $P < 0.01$. C and D: Plasma CRP levels and PWV in the nonresponders and responders before and 3 months after treatment with pioglitazone. Each column and bar represents the mean \pm SEM before (B) and after 3 months (A). * $P < 0.05$; ** $P < 0.01$.

ates: Δ HbA_{1c}, Δ HOMA-IR, Δ BMI, Δ SBP, Δ DBP, Δ LDL, and Δ triglycerides. All statistical analyses were performed using the Stat View program version 5.0 for Windows (SAS Institute).

RESULTS

Baseline profiles of the pioglitazone-treated and control groups

There was no significant difference between the pioglitazone-treated and control groups in age, sex ratio, BMI, SBP, DBP, FPG, HbA_{1c}, IRI, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides before the pioglitazone treatment (Table 1). The two groups did not differ significantly in plasma adiponectin and leptin concentrations (Table 1) and CRP and PWV (Fig. 1) at baseline.

Effects of pioglitazone treatment in all the study subjects

In the control group, BMI, SBP, DBP, FPG, HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides remained unchanged during this study (Table 2). There were no significant changes in plasma adiponectin and leptin concentrations and CRP and PWV in the control group during this study (Table 2, Fig. 1).

After treatment with pioglitazone, FPG, HbA_{1c}, HOMA-IR, and LDL cholesterol decreased significantly (FPG, HbA_{1c}, and HOMA-IR, $P < 0.01$; LDL cholesterol, $P < 0.05$), whereas BMI, SBP, DBP, total cholesterol, HDL cholesterol, and triglycerides remained unchanged (Table 2). IRI tended to decrease in the pioglitazone-treated group but did not reach statistical significance. Plasma adiponectin concentrations increased significantly after treatment with pioglitazone ($P < 0.01$). In this study, plasma leptin concentrations did not change after pioglitazone treatment.

Effects of pioglitazone treatment in the nonresponders and responders

On average, the responders in the pioglitazone-treated group showed a significant decrease in HbA_{1c} (Δ HbA_{1c} = $1.5 \pm 0.1\%$; $P < 0.01$), although it did not decrease significantly after treatment in the nonresponders (Table 3). Accordingly, after treatment with pioglitazone, FPG was significantly decreased in the responders ($P < 0.01$), and this was associated with a significant reduction of HOMA-IR ($P < 0.01$). By contrast, HOMA-IR was reduced only slightly in the nonresponders ($P < 0.05$). In this study, total cholesterol, LDL cholesterol,

Table 2—Results of 3-month additional treatment with pioglitazone in the study patients

Variables	Control (n = 66)		Pioglitazone (n = 70)	
	Baseline	3 months	Baseline	3 months
BMI (kg/m ²)	23.0 ± 0.5	23.2 ± 0.5	23.4 ± 0.4	23.5 ± 0.4
SBP (mmHg)	146 ± 2	146 ± 3	144 ± 2	145 ± 2
DBP (mmHg)	82 ± 2	82 ± 2	81 ± 2	81 ± 2
FPG (mmol/l)	9.4 ± 0.3	9.2 ± 0.3	9.6 ± 0.4	8.0 ± 0.3†§
HbA _{1c} (%)	8.0 ± 0.2	7.9 ± 0.2	8.1 ± 0.1	7.1 ± 0.1†§
IRI (pmol/l)	55.9 ± 4.10	54.9 ± 4.10	57.5 ± 3.96	51.7 ± 5.18
HOMA-IR	3.30 ± 0.28	3.20 ± 0.29	3.35 ± 0.29	2.25 ± 0.17†§
Total cholesterol (mmol/l)	5.45 ± 0.16	5.46 ± 0.17	5.46 ± 0.10	5.33 ± 0.10
LDL cholesterol (mmol/l)	3.32 ± 0.11	3.33 ± 0.12	3.30 ± 0.08	3.17 ± 0.08*
HDL cholesterol (mmol/l)	1.47 ± 0.10	1.43 ± 0.11	1.44 ± 0.05	1.47 ± 0.05
Triglycerides (mmol/l)	1.55 ± 0.04	1.57 ± 0.06	1.56 ± 0.04	1.50 ± 0.04
Adiponectin (μg/ml)	6.08 ± 0.42	6.06 ± 0.39	6.03 ± 0.34	7.82 ± 0.52†‡
Leptin (ng/ml)	6.56 ± 0.45	6.58 ± 0.45	6.52 ± 0.50	6.63 ± 0.46

Data are means ± SEM. * $P < 0.05$, † $P < 0.01$ vs. baseline values; ‡ $P < 0.05$, § $P < 0.01$ vs. control.

and triglycerides decreased significantly in the responders ($P < 0.05$) but not in the nonresponders (Table 3).

Before treatment with pioglitazone, no significant difference in CRP was noted between the nonresponders and responders (Fig. 1). CRP decreased significantly in both the nonresponders and responders 3 months after treatment (nonresponders, $0.15 \pm 0.01 \rightarrow 0.11 \pm 0.01$ mg/dl, $P < 0.01$; responders, $0.14 \pm 0.01 \rightarrow 0.10 \pm 0.01$ mg/dl, $P < 0.01$), and the decrease in CRP was significantly greater in the responders than in the nonresponders ($P < 0.05$) (Fig. 1). After treatment with pioglitazone, PWV was significantly reduced

in both the nonresponders and responders (nonresponders, $1,658 \pm 40 \rightarrow 1,618 \pm 40$ cm/s, $P < 0.01$; responders, $1,678 \pm 48 \rightarrow 1,607 \pm 46$ cm/s, $P < 0.01$). There was no significant difference in PWV between the nonresponders and responders 3 months after treatment (Fig. 1).

Before treatment, there was no significant difference in plasma adiponectin concentration between the nonresponders and responders (Table 3). Plasma adiponectin concentrations increased significantly in both the responders and nonresponders (nonresponders, $5.98 \pm 0.52 \rightarrow 7.48 \pm 0.71$ μg/ml, $P <$

0.01 ; responders, $6.07 \pm 0.46 \rightarrow 8.08 \pm 0.73$ μg/ml, $P < 0.01$). Before treatment, plasma leptin concentrations were slightly higher in the responders than in the nonresponders. After treatment, plasma leptin concentrations remained unchanged in both subgroups.

Analysis of the association of Δ PWV with Δ adiponectin, Δ CRP, and other variables

In the control and pioglitazone-treated groups, analysis of Pearson's correlation revealed that Δ PWV significantly correlated only with Δ CRP ($r = 0.285$) and Δ adiponectin ($r = -0.318$) (data not

Table 3—Results of 3-month additional treatment with pioglitazone in the study patients divided into two subgroups

Variables	Nonresponders (n = 30)		Responders (n = 40)	
	Baseline	3 months	Baseline	3 months
Sex (male/female)	12/18		20/20	
Age (years)	60.4 ± 2.1		61.8 ± 1.6	
BMI (kg/m ²)	22.7 ± 0.6	23.0 ± 0.6†	23.9 ± 0.5	23.9 ± 0.5
SBP (mmHg)	144 ± 4	143 ± 3	144 ± 3	146 ± 3
DBP (mmHg)	80 ± 2	80 ± 2	82 ± 2	83 ± 3
FPG (mmol/l)	9.4 ± 0.5	8.9 ± 0.4	9.7 ± 0.5	7.3 ± 0.4†‡
HbA _{1c} (%)	7.8 ± 0.2	7.7 ± 0.2	8.3 ± 0.1‡	6.8 ± 0.1†‡
IRI (pmol/l)	49.7 ± 4.96	46.8 ± 4.75	63.3 ± 5.76	55.5 ± 8.42
HOMA-IR	2.96 ± 0.38	2.62 ± 0.31*	3.65 ± 0.42	1.97 ± 0.16†‡
Total cholesterol (mmol/l)	5.40 ± 0.12	5.42 ± 0.11	5.51 ± 0.15	5.27 ± 0.16*
LDL cholesterol (mmol/l)	3.32 ± 0.09	3.27 ± 0.09	3.30 ± 0.11	3.09 ± 0.12*
HDL cholesterol (mmol/l)	1.37 ± 0.08	1.43 ± 0.08	1.50 ± 0.07	1.51 ± 0.07
Triglycerides (mmol/l)	1.54 ± 0.06	1.56 ± 0.05	1.57 ± 0.05	1.46 ± 0.06*
Adiponectin (μg/ml)	5.98 ± 0.52	7.48 ± 0.71†	6.07 ± 0.46	8.08 ± 0.73†
Leptin (ng/ml)	6.16 ± 0.79	6.21 ± 0.77	6.79 ± 0.66	6.95 ± 0.56

Data are means ± SEM. * $P < 0.05$, † $P < 0.01$ vs. baseline values; ‡ $P < 0.05$ vs. nonresponders.

Table 4—ANCOVA models showing the differences associated with treatment with pioglitazone in CRP, PWV, and adiponectin

Variables with pioglitazone treatment	Covariates	Regression coefficient (SEM)	P value
Δ CRP	Unadjusted	−0.018 (0.010)	0.0262
	Adjusted for Δ HbA _{1c}	−0.041 (0.013)	0.0015
	Δ HOMA-IR	−0.027 (0.010)	0.0117
	Δ BMI	−0.042 (0.010)	0.0001
Δ PWV	Unadjusted	−51.94 (21.61)	0.0180
	Adjusted for Δ HbA _{1c}	−50.64 (27.99)	0.0423
	Δ HOMA-IR	−47.03 (23.31)	0.0463
	Δ sBP and Δ dbP	−69.49 (26.87)	0.0112
	Δ LDL	−54.29 (21.89)	0.0147
	Δ Triglycerides	−49.89 (21.75)	0.0238
	Δ CRP	−34.56 (23.12)	0.1381
	Δ Adiponectin	−29.99 (22.47)	0.1850
Δ Adiponectin	Unadjusted	1.808 (0.474)	0.0002
	Adjusted for Δ HbA _{1c}	1.522 (0.616)	0.0151
	Δ HOMA-IR	0.547 (0.147)	0.0003

Changes in variables are indicated by subtracting the pretreatment value from the post-treatment value.

shown). We also examined the significance of pioglitazone regarding Δ CRP, Δ adiponectin, and Δ PWV as dependent variables using ANCOVA models that include Δ HbA_{1c} and Δ HOMA-IR as covariates. As shown in Table 4, after adjustment for Δ HbA_{1c} and Δ HOMA-IR, ANCOVA revealed that treatment with pioglitazone was associated with Δ CRP and Δ adiponectin. Furthermore, the pioglitazone treatment was associated with Δ PWV, dependent on only Δ CRP and Δ adiponectin, irrespective of Δ HbA_{1c}, Δ HOMA-IR, Δ blood pressure, Δ LDL cholesterol, and Δ triglycerides in the whole subjects. In the nonresponders and responders separately, Δ PWV with pioglitazone treatment was associated with only Δ adiponectin (multivariate regression coefficient, -11.4 , $P = 0.042$), irrespective of Δ HbA_{1c} (19.2 , $P = 0.5235$), Δ LDL cholesterol (0.94 , $P = 0.2111$), and Δ CRP (383.1 , $P = 0.1827$) (data not shown).

CONCLUSIONS— Type 2 diabetic patients are at an increased risk of developing atherosclerosis. Because of their antiatherogenic and antidiabetic effects, TZDs may offer a novel therapeutic strategy to treat diabetes-associated cardiovascular disease in type 2 diabetic patients, beyond glycemic control. Several lines of in vitro and in vivo evidence have indicated that the antiatherogenic effect of TZDs is mediated primarily through a di-

rect action on the vasculature (9–18). However, whether TZDs can exert the antiatherogenic effect independently of the antidiabetic effect has never been addressed in humans. The aim of this study was to elucidate the relationship between the antiatherogenic and antidiabetic effects of pioglitazone in type 2 diabetic patients.

As for its antiatherogenic effects, this study demonstrated that pioglitazone decreased significantly CRP in patients with type 2 diabetes, which is consistent with previous reports (32). Furthermore, we also observed that treatment with pioglitazone for 3 months resulted in a significant decrease in PWV. This is in agreement with that of Minamikawa et al. (19) and Koshiyama et al. (20), who reported that IMT was significantly reduced in type 2 diabetic patients administered troglitazone or pioglitazone for 3 months. Taniwaki et al. (33) previously demonstrated that there is a good correlation between carotid arterial IMT and PWV in type 2 diabetic patients. In addition, recent studies have demonstrated that PWV is not only a marker of vascular damages (34) but also a prognostic predictor of mortality in diabetes (28). Therefore, we believe that combined with other markers of atherosclerosis such as high-sensitivity CRP, PWV can serve as a reliable marker for the evaluation of the antiatherogenic effect of pioglitazone. The crucial observation in this study is that pioglitazone

decreases CRP and PWV in both the non-responders and the responders with respect to its antidiabetic effect. Furthermore, multivariate analysis revealed that Δ CRP and Δ PWV are independent of the changes in parameters related to glucose metabolism, i.e., Δ FPG, Δ IRI, Δ HbA_{1c}, and Δ HOMA-IR. Especially in the whole subjects, Δ PWV with the pioglitazone treatment is associated with only Δ CRP and Δ adiponectin, irrespective of Δ HbA_{1c} and Δ LDL cholesterol. These findings indicate that pioglitazone is capable of preventing the progression of atherosclerosis independent of the improvement of glucose metabolism; it is likely that the antiatherogenic effect of pioglitazone is not mediated through its antidiabetic effect. In this regard, Minamikawa et al. (19) reported that both HbA_{1c} and postprandial triglycerides levels decreased in type 2 diabetic patients treated with troglitazone, although there were no significant correlations between the changes in the above parameters and Δ IMT. It is known that PPAR- γ is expressed in vascular cells, such as endothelial cell, VSMCs, and macrophages, and it may play a protective role in the development of atherosclerosis (9–15,35,36). We postulate that in humans as well, the antiatherogenic effect of pioglitazone is mediated primarily by its direct action on the vasculature.

It was demonstrated that TZDs activate PPAR- γ expressed abundantly in the adipose tissue where it regulates the production of various adipocyte-derived hormones (collectively called adipocytokines) (37), such as leptin and adiponectin. In this study, TZDs significantly increased the plasma concentrations of adiponectin in type 2 diabetic patients, which is consistent with the findings of several previous reports (38,39,44). It is of particular interest to note that pioglitazone can increase plasma adiponectin concentrations, irrespective of the responsiveness to its antidiabetic effect. Recent studies with adiponectin-deficient mice have revealed that it plays a protective role in the development of atherosclerosis (40,41). Furthermore, decreased production of adiponectin is associated with atherosclerotic disease (42,43). Collectively, we postulate that TZDs can exert the antiatherogenic effect at least partly through the induction of adiponectin production/secretion in the adipose tissue.

Interestingly, we found that CRP was significantly reduced in the responders relative to nonresponders. These observations suggest that some of the antiatherogenic effects of pioglitazone are associated with the improvement of glucose metabolism. In this study, no significant difference in Δ PWV was noted between the nonresponders and responders. We speculate that CRP may represent an acute inflammatory process in the vasculature (or fatty degeneration), thus being improved by the 3-month treatment with pioglitazone. On the other hand, PWV may reflect advanced sclerotic changes in the vasculature (or vascular stiffness), thus taking more time to be improved. The data of this study also suggest that CRP might be more sensitive to the acute metabolic changes induced by TZDs than PWV. Further studies are necessary to validate the above aspects.

HDL cholesterol was unchanged in both the nonresponders and responders throughout this study, which is consistent with previous studies (44). In this study, pioglitazone significantly decreased triglycerides not in the nonresponders but in the responders. Improved insulin resistance by pioglitazone might reduce triglyceride levels in the responders than in the nonresponders.

This study is observational and non-randomized. However, the patients in the control group and treatment group were well matched for age, sex ratio, BMI, SBP, DBP, FPG, HbA_{1c}, IRI, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, before the pioglitazone treatment. Also, the treatment group included all diabetic patients who had been treated with pioglitazone. Thus, it provides important insights into the treatment and outcome of patients treated with pioglitazone. It was reported that there are responders and nonresponders to treatment with TZD (23,24), thus we also divided the patients into responders and nonresponders.

In conclusion, we demonstrated that pioglitazone can exert its antiatherogenic effect in type 2 diabetic patients, irrespective of responsiveness to its antidiabetic effect. This study suggests the usefulness of pioglitazone as a multiple-benefit drug that exerts on hypoglycemic effect and protects the patient from multiple risk factors. The data of this study suggest that the antiatherogenic effect of pioglitazone

results largely from its direct action on the vasculature.

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