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The effects of pioglitazone on cerebrovascular resistance in patients with type 2 diabetes mellitus

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Abstract

Atherosclerosis is one of the major causes of morbidity and mortality in patients with type 2 diabetes mellitus. Pioglitazone has been reported to have antiatherogenic effects. The aim of this study was to investigate whether pioglitazone affects pulsatility index (PI) of the cerebral arteries and the carotid intima-media thickness in type 2 diabetic patients. A total of 40 type 2 diabetic patients were included in this study. They were divided into 2 groups: the pioglitazone-treated group (pioglitazone 15 mg/d with gliclazide 80-320 mg/d for 12 weeks) and the gliclazide-treated group (gliclazide 80-320 mg/d for 12 weeks). Transcranial Doppler ultrasonography was performed for each cerebral artery, and PI was calculated as (systolic velocity − diastolic velocity)/mean velocity. The pioglitazone treatment significantly increased high-density lipoprotein cholesterol and decreased triglyceride levels and insulin resistance. This study revealed that the change in mean intima-media thickness was not significant in both groups, but the change in PI was significantly decreased with pioglitazone compared to gliclazide. In conclusion, pioglitazone decreased PI and improved cerebrovascular resistance in type 2 diabetic patients.
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1. Introduction

Patients with type 2 diabetes mellitus (DM) are at high risk for coronary heart disease, cerebrovascular disease or stroke, and peripheral vascular disease. Their risk for these disorders is 2- to 6-fold higher than that in persons without diabetes [1]. These macrovascular diseases are common causes of morbidity and mortality among people with diabetes.

Thiazolidinediones, including pioglitazone, improve insulin sensitivity and glycemic control in type 2 diabetic patients. In addition, patients treated with thiazolidinediones show improved endothelial function, decreased inflammation, and decreased plasma free fatty acid levels, which may have beneficial antiatherogenic effects [2-4].

In recent years, noninvasive, high-resolution, B-mode ultrasound methods have been developed to measure the intima-media thickness (IMT) of the carotid artery as an index for early atherosclerosis. Arterial wall IMT has been established by many studies to be an early marker and predictor of atherosclerotic disease [5]. A thickened carotid intima-media layer correlates not only with the presence of cardiovascular risk factors but also with the risk of future macrovascular events, such as myocardial infarction and stroke [6-8]. Some investigators have reported that pioglitazone decreased IMT in patients with type 2 DM [9-12].

Diabetes mellitus is a major risk factor for ischemic stroke [13]. Diabetic patients have twice the incidence of stroke compared with nondiabetic patients [14], but clinicians have yet to reach consensus on optimal screening methods for cerebrovascular complications. Previously, clinical attempts to detect subclinical cerebrovascular changes related to DM had been performed by the use of single-photon emission computed tomography [15,16], xenon-computed tomography [17,18], and positron emission tomography [19], but these methods failed to provide consistent results. In addition, the cost of magnetic resonance angiography (MRA) is high; therefore, MRA is not suitable as a screening test. In contrast, transcranial

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Doppler ultrasonography (TCD), because it is noninvasive and easily applicable, appears to be more suitable as a screening tool than previous methods. Nevertheless, studies involving the application of TCD to diabetic patients have rarely been reported. By performing TCD, the hemodynamic rates were measured, and by calculation, the pulsatility index (PI) and the resistance index could be obtained. Among them, the PI reflects the vascular resistance in the peripheral area of the cerebral blood vessels where the test was performed. It has been reported that in stroke-free, normotensive diabetic patients, in comparison with healthy individuals, the PI is increased, and it shows an increasing trend in proportion to age and the duration of diabetes [20].

That thiazolidinediones reduced carotid IMT has been known to be associated with cerebrovascular diseases, but little is known about the effects of thiazolidinediones on the PI of cerebral arteries in type 2 DM.

The aim of the present study was to investigate whether pioglitazone affects the carotid IMT and PI of cerebral arteries in type 2 diabetic patients.

2. Patients and methods

2.1. Patients

The study subjects included 40 orally treated patients with type 2 DM who had never received thiazolidinediones. The patients were consecutively randomized to receive either pioglitazone 15 mg/d plus gliclazide 80 to 320 mg/d (n = 20) or gliclazide 80 to 320 mg/d (n = 20) for 12 weeks titrated for optimal glycemic control. The selection criteria for patients were as follows: (1) previously known type 2 diabetic mellitus treated with oral antidiabetic agents; (2) no significant hepatic (alanine aminotransferase or aspartate aminotransferase >2.5-fold the normal value) or renal (serum creatinine >1.5mg/dL) disease, absence of congestive heart failure (New York Heart Association class II-IV), and no known carotid artery stenosis. This study was approved by our human research ethics committees. Informed consent was obtained from each participant.

Patients were enrolled after a first screening visit. All study measurements were obtained on study entry and at the end of an observation period of 12 weeks. Individual medical advice was given to every patient at the beginning and offered throughout the duration of the study to optimize glycemic control. The gliclazide dose was titrated to 80 mg and subsequently to 320 mg at 6-week visit.

2.2. Biochemical parameters

All measurements were obtained in the morning, after the patient had fasted since midnight. Blood samples were immediately centrifuged, and plasma and serum samples were kept at −70°C until laboratory testing. Hemoglobin A_{1c} (HbA_{1c}) was determined by means of high-performance liquid chromatography (Variant II, Bio-Rad, Hercules, CA). Glucose was measured with a standard glucose oxidase reference method (747 Automatic Analyzer, Hitachi, Tokyo, Japan). Fasting serum insulin was determined by means of chemiluminescence (radioimmunoassay kit, Daiichi, Tokyo, Japan). Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were measured with an enzymatic color test (Hitachi 747, Daiichi). Low-density lipoprotein cholesterol was calculated according to the Friedewald formula. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) analysis and assessed by Kitt [21,22].

$$\text{Kitt (rate constant for plasma glucose disappearance)} = 0.693/t_{1/2}{*}100(\%/\text{min})$$

$$HOMA-IR = \text{fastinginsulin}\ (\mu\text{U/mL}) \times \text{fastingplasmaglucose(mmol/L)}/22.5$$

2.3. Carotid IMT

The carotid IMT was evaluated 2 times by a single operator at an interval of 12 weeks with high-resolution B-mode ultrasonography on a single machine (Toshiba SSA-270A, Tokyo, Japan) with a 7.5-MHz linear array transducer. All recordings were obtained with the patient resting in a supine position, with the head turned slightly to the contralateral side. Intima-media thickness was defined as the distance between the lumen intima interface and the media adventitia interface. Measurements of the carotid IMT were conducted at 3 differential plaque-free sites: the site of the greatest thickness and 2 other points, 1 cm upstream and 1 cm downstream from the site of the greatest thickness. The mean of the 3 determinations of right and left IMT was defined as mean IMT. Plaques, defined as a local thickness of more than 2 mm, were documented.

2.4. Transcranial Doppler ultrasonography

All TCD studies were performed 2 times by a single operator at an interval of 12 weeks, with a 3-dimensional mapping instrument (Trans-scan, EME, Uberlingen, Germany) and examination techniques similar to those previously described [18]. Doppler signals from the main stem of the middle cerebral artery (MCA) were obtained with a 2-MHz probe, attached to a stereotactic headpiece, through a transtemporal window at a depth of 50 to 60 mm. Those from the basilar artery (BA) were obtained with a 2-MHz handheld probe below the occiput at a depth of 80 to 90 mm. For each artery, the mean, systolic, and diastolic velocities were measured, and the Gosling PI was calculated automatically as (systolic velocity − diastolic velocity)/mean velocity [20]. At least 3 measurements were performed at a similar depth for each artery, and the median value was selected and used in this study. All other major intracranial cerebral arteries were also examined by TCD to exclude the possibility of major vascular lesion involvement in those vessels.

Table 1
Baseline clinical characteristics of study subjects

	PIO-treated group	Control group
No. of patients	20	20
Sex (M/F)	11/9	12/8
Age (y)	63.1 ± 7.2	64.2 ± 7.1
BMI (kg/m^2)	24.3 ± 4.1	24.1 ± 3.0
DM duration (y)	7.4 ± 7.2	7.9 ± 6.2
Systolic BP (mm Hg)	135.2 ± 21.1	138.1 ± 18.1
Diastolic BP (mm Hg)	85.8 ± 16.2	88.2 ± 17.6
Current smoking (%)	6 (30)	7 (35)
PHx of CVD (%)	3 (15)	3 (15)
PHx of CAOD (%)	2 (10)	2 (10)

PIO indicates pioglitazone; BMI, body mass index; BP, blood pressure; PHx, past history; CVD, cerebrovascular disease; CAOD, coronary artery occlusive disease. There were no statistically significant differences between the groups ($P > .05$).

Among the several arteries examined, the MCA and the BA, intracranial arteries where the test could be performed relatively uniformly, were selected as the subject cerebral arteries for analysis.

2.5. Statistical analysis

Data are expressed as mean ± SD. Statistical analysis was performed with unpaired or paired Student t test. The χ^2 test was performed to compare the distribution of nonparametric data. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Both treatment groups were similar with respect to age, sex distribution, duration of DM, glycemic status, presence of cardiovascular and cerebrovascular diseases, hypertension, smoking status, baseline insulin sensitivity, carotid IMT, and cerebral PI. Concomitant treatments with antiplatelets, rennin-angiotensin system inhibition, and statin drugs, all of which might affect insulin sensitivity, IMT, and PI, were equally distributed in both groups at the start and end of the study (Table 1).

Table 3
Changes in IMT

	PIO-treated group (n = 20)		Control group (n = 20)	
	Before	After	Before	After
Lt mean IMT (mm)	0.91 ± 0.03	0.91 ± 0.01	0.92 ± 0.03	0.93 ± 0.01
Rt mean IMT (mm)	0.83 ± 0.03	0.82 ± 0.01	0.87 ± 0.03	0.89 ± 0.01
Lt max IMT (mm)	1.15 ± 0.05	1.09 ± 0.02 *	1.07 ± 0.05	1.05 ± 0.02
Rt max IMT (mm)	1.02 ± 0.04	0.93 ± 0.04 *	0.96 ± 0.04	0.96 ± 0.04

Lt indicates left; Rt, right; max, maximum.
* $P < .01$ before vs after treatment in the pioglitazone group.

3.2. Changes in biochemical characteristics

After 12 weeks, the fasting glucose levels, postprandial glucose, and HbA_{1c} decreased by a similar magnitude in the pioglitazone and gliclazide groups. Fasting insulin concentrations, free fatty acids (FFA), and TG decreased significantly only in the pioglitazone group, whereas they remained constant in the gliclazide group. High-density lipoprotein cholesterol increased in the pioglitazone group. Homeostasis model assessment of insulin resistance score was reduced and Kitt increased in the pioglitazone group, whereas no change occurred in the gliclazide group (Table 2).

3.3. Carotid IMT

Intima-media thickness changed little after treatments in the gliclazide group, maximum IMT in the pioglitazone

Table 2
Changes in clinical and biochemical characteristics

	PIO-treated group (n = 20)		Control group (n = 20)	
	Before	After	Before	After
BMI (kg/m^2)	24.3 ± 4.1	25.1 ± 4.0	24.1 ± 3.0	24.7 ± 3.3
Systolic BP (mm Hg)	135.2 ± 31.1	135.2 ± 26.4	138.1 ± 28.1	135.3 ± 25.8
Diastolic BP (mm Hg)	85.8 ± 16.2	84.5 ± 18.3	88.2 ± 17.6	85.6 ± 19.3
Fasting glucose (mmol/L)	9.85 ± 1.27	7.95 ± 1.03 *	9.51 ± 0.96	7.47 ± 0.74 *
PP 2-h glucose (mmol/L)	12.44 ± 2.40	10.32 ± 1.93 *	12.64 ± 1.05	10.47 ± 0.94 *
HbA_{1c} (%)	9.0 ± 2.3	7.1 ± 1.3 *	8.8 ± 2.2	7.1 ± 1.2 *
TC (mmol/L)	5.22 ± 0.69	5.18 ± 0.68	5.10 ± 0.71	5.06 ± 0.74
TG (mmol/L)	2.24 ± 0.41	1.87 ± 0.41 *	2.10 ± 0.42	1.97 ± 0.26
HDL-C (mmol/L)	0.92 ± 0.20	1.02 ± 0.16 *	0.88 ± 0.18	0.91 ± 0.21
LDL-C (mmol/L)	3.85 ± 0.44	3.79 ± 0.47	3.80 ± 0.53	3.75 ± 0.46
FFA (mmol/L)	0.68 ± 0.25	0.56 ± 0.22 *	0.66 ± 0.30	0.62 ± 0.21
Insulin (μIU/mL)	20.22 ± 8.35	12.94 ± 5.31 *	20.77 ± 6.29	18.17 ± 6.82
Fibrinogen (g/L)	4.32 ± 0.83	3.98 ± 0.81	4.21 ± 0.91	3.96 ± 0.81
PAI-1 (ng/mL)	43.1 ± 7.3	36.2 ± 9.5	43.9 ± 7.3	37.2 ± 6.1
Kitt (%/min)	1.3 ± 0.7	1.9 ± 1.0 *	1.3 ± 1.1	1.5 ± 0.9
HOMA-IR	9.75 ± 3.12	6.24 ± 3.98 *	9.70 ± 1.14	8.52 ± 4.87

TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol.
* $P < .05$ before vs after treatment in each group.

Table 4
Changes in TCD parameters

	PIO-treated group (n = 20)		Control group (n = 20)	
	Before	After	Before	After
Rt MCA				
Vm (cm/s)	54.6 ± 14.7	57.3 ± 10.7	55.4 ± 13.8	57.1 ± 16.5
Vs (cm/s)	83.1 ± 11.0	82.6 ± 9.9	85.3 ± 20.2	83.2 ± 13.6
Vd (cm/s)	36.7 ± 13.3	38.5 ± 12.8	37.1 ± 11.5	34.1 ± 17.2
PI	0.85 ± 0.16	0.77 ± 0.13 *	0.87 ± 0.17	0.86 ± 0.15
Lt MCA				
Vm (cm/s)	57.0 ± 12.1	58.4 ± 13.5	54.7 ± 11.0	55.9 ± 15.8
Vs (cm/s)	84.0 ± 15.7	81.2 ± 10.7	83.6 ± 17.5	84.3 ± 10.9
Vd (cm/s)	35.5 ± 11.3	37.4 ± 12.8	36.6 ± 9.8	35.4 ± 12.2
PI	0.86 ± 0.14	0.76 ± 0.17 *	0.86 ± 0.20	0.88 ± 0.13
BA				
Vm (cm/s)	43.0 ± 10.1	44.5 ± 11.5	44.2 ± 11.9	46.1 ± 16.0
Vs (cm/s)	62.8 ± 10.6	61.2 ± 15.2	63.2 ± 19.4	64.7 ± 15.1
Vd (cm/s)	23.2 ± 7.1	23.4 ± 9.6	22.7 ± 12.3	22.3 ± 9.5
PI	0.92 ± 0.24	0.85 ± 0.25 *	0.91 ± 0.17	0.90 ± 0.21

Vm indicates mean velocity; Vs, systolic velocity; Vd, diastolic velocity.
* $P < .05$ before vs after treatment in each group.

group significantly decreased, but mean IMT change was not statistically significant (Table 3).

3.4. Cerebral PI

BA PI and MCA PI were decreased significantly in the pioglitazone group, whereas no significant change was noted in the gliclazide group (Table 4, Fig. 1).

4. Discussion

There has been increasing evidence that thiazolidinediones, including pioglitazone, cause an inhibition of early atherosclerotic processes by peroxisome proliferator–activated receptor (PPAR)–γ activation, and these PPARs exert their inflammatory activities in vascular and immunologic cell types, such as endothelial cells, vascular smooth muscle cells, and monocytes/macrophages [23]. Peroxisome proliferator–activated receptor γ agonists, such as pioglitazone, have emerged as potential tools to modulate the inception and progression of atherosclerosis at the level of the arterial wall [24]. Pioglitazone has a beneficial effect on the prevention and treatment of atherosclerotic vascular complications of type 2 DM, and in fact, it has been reported that treatment with pioglitazone for 24 weeks decreased carotid IMT in patients with type 2 DM [9-12].

Ischemic stroke, which is readily measured by the noninvasive TCD, is a major atherosclerotic complication in diabetes. Pioglitazone has been reported to have antiatherogenic effects in patients with type 2 DM. Thus, we administered pioglitazone for 12 weeks and measured the carotid IMT and the PI that reflect cerebrovascular resistance.

The Gosling PI was originally designed to measure vascular resistance, and this relationship was demonstrated in the brachial artery of healthy humans [20]. Thus, the

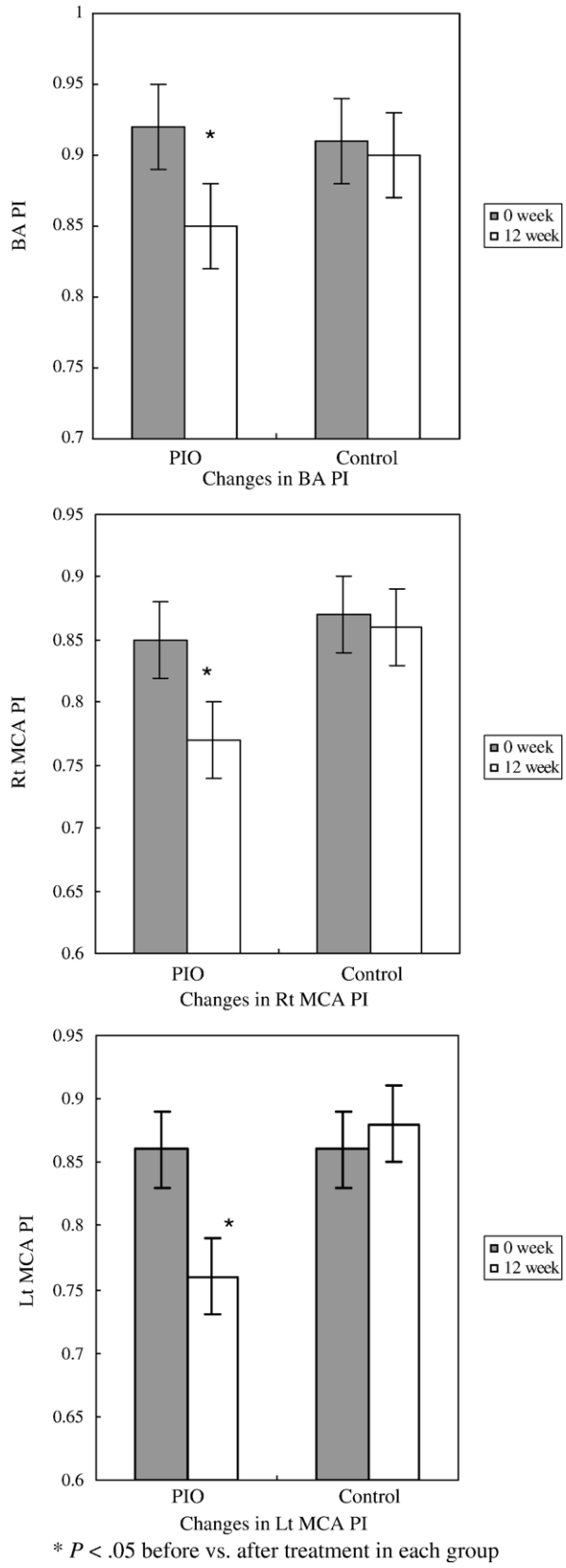

Fig. 1. BA PI and MCA PI are decreased significantly in the pioglitazone-treated group. * $P < .05$ before vs after treatment in each group.

increased PI observed in this study presumably represents enhanced cerebrovascular resistance in the cerebral circulation and the decreased PI represents improved cerebrovascular resistance, and the present study confirmed that pioglitazone improves cerebrovascular resistance.

Both the pioglitazone and gliclazide groups had comparable HbA_{1c} values before and after the study. However, glycemic control as determined by HbA_{1c} was not different between the groups. Therapy with pioglitazone for 12 weeks decreased PI in patients with type 2 DM, and this effect was independent of glycemic control. The findings of this study imply that improved glycemic control is unlikely to be the cause of PI decrease. There are other confounding factors as well, such as renin-angiotensin system inhibition, statin treatment, antiplatelet treatment, smoking status, hypertension, and duration of diabetes, which were well controlled in this study by equal distribution among the treatment groups.

As expected, based on a review of previous trials [11], in the present study, the change in plasminogen activator inhibitor 1 (PAI-1) and fibrinogen levels was not significant after pioglitazone treatment. According to recent studies, however, therapy with pioglitazone for 12 months decreased PAI-1 levels [25].

Our data are similar to the available reports on the efficacy of pioglitazone; pioglitazone induced a significant decrease in TG levels, FFA, and insulin resistance and a significant increase in HDL-C levels [26-28]. In the gliclazide group, a decreasing trend toward insulin resistance was shown; nonetheless, it was not statistically significant and was considered to be the secondary result of the improved glycemic control.

In the gliclazide group, the carotid IMT was slightly increased or was not changed. In the pioglitazone group, although maximum IMT significantly decreased, mean IMT change was not statistically significant. It was considered that the study period was too short and the dose of pioglitazone was too small to assess the evident change in carotid IMT. In another study, treatment with 30 or 45 mg pioglitazone for 24 weeks led to a significant decrease in carotid mean IMT [9-12]. Like any other study, our study has limitations. The sample size is relatively small with a wide age range. Therefore, the change in carotid IMT may become statistically significant if a larger number of patients or high dose of pioglitazone was studied for a longer period.

The PI evaluated by TCD was significantly decreased in the pioglitazone group, whereas no significant change was noted in the gliclazide group, which shows that pioglitazone improves cerebrovascular resistance.

Taken together with our findings, pioglitazone seems to exert antiatherogenic effects through a multitude of mechanisms, including a decrease in insulin resistance, inhibition of atherogenic processes, and reduction of cardiovascular risk factors. From the review of recent animal studies, during cerebral ischemic damage, it was found that infarction size in the group of PPAR-γ agonists was smaller than that in the control group; inflammation markers, such as superoxide dismutase, nitric oxide synthase, interleukin 1β, and cyclooxygenase-2, may be involved in these results [29,30]. The present study cannot distinguish between the possible mechanisms or explain the pathogenic principle underlying the reduction of cerebral PI. More studies are necessary to elucidate the biochemical interactions.

In conclusion, we have shown that treatment with pioglitazone for 12 weeks led to a significant decrease in cerebral PI in patients with type 2 DM. The effect is independent of glycemic control, suggesting that pioglitazone may be useful in the improvement of cerebrovascular resistance.

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