Effect of Pioglitazone on Carotid Intima-Media Thickness and Arterial Stiffness in Type 2 Diabetic Nephropathy Patients

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Atherosclerosis is the major cause of morbidity and mortality in patients with type 2 diabetes, and pioglitazone has been reported to have anti-inflammatory and potential antiatherogenic effects. The aim of the present study was to determine whether pioglitazone, glibenclamide, or voglibose affects carotid intima-media thickness (IMT), pulse wave velocity (PWV), and urinary albumin excretion (UAE) in normotensive type 2 diabetic nephropathy patients. Forty-five normotensive type 2 diabetes patients with microalbuminuria were randomized to 12-month treatment with pioglitazone (30 mg/d, n = 15), glibenclamide (5 mg/d, n = 15), or voglibose (0.6 mg/d, n = 15). Pre- and posttreatment UAE, PWV, and IMT values were compared between treatment groups and a group of age-matched healthy control subjects (n = 30). Pretreatment PWV, IMT, and UAE values differed little between the 3 groups, but UAE was greater in the 45 type 2 diabetes patients (132.5 ± 36.4 μg/min) than in the control subjects (6.2 ± 1.8 μg/min, $P < .001$). IMT (0.76 ± 0.12 mm) was significantly greater in the diabetics than in the controls (0.60 ± 0.08 mm, $P < .01$). PWV (1,840 ± 320 cm/s) was also significantly greater in the diabetics than in the controls (1,350 ± 225 cm/s, $P < .01$). After 6 and 12 months, UAE, IMT, and PWV in the pioglitazone treatment group were significantly lower than those in the glibenclamide treatment group and voglibose treatment group (UAE: 6 months, $P < .05$ and 12 months, $P < .01$; IMT and PWV: 6 months, $P < .05$ and 12 months, $P < .05$). Pioglitazone, but not glibenclamide or voglibose, appears to be effective in reducing UAE, IMT, and PWV in normotensive type 2 diabetes patients with microalbuminuria.

IMPROVEMENT IN cardiovascular risk factors may be critical in treating patients with type 2 diabetes, given that macrovascular disease is the major cause of morbidity and mortality in such patients.[1] Thiazolidinediones, including pioglitazone, improve insulin sensitivity and glycemic control in type 2 diabetes patients. In addition, improved endothelial function, decreased inflammation, decreased plasma free fatty acid levels, and decreased blood pressure have been observed, which may have important beneficial effects on the vasculature.[2] Pioglitazone has been shown in vivo to have protective effects against both acute and chronic vascular injury through inhibition of vascular smooth muscle cell proliferation.[3] In addition, we and other investigators have shown that pioglitazone administration decreases urinary albumin excretion (UAE) in diabetic rats and humans, suggesting the novel therapeutic action of pioglitazone on diabetic nephropathy.[4,5] Bakris et al[6] reported that rosiglitazone treatment was associated with a decrease in UAE in patients with type 2 diabetes. Intima-media thickness (IMT) of the carotid arteries is related to coronary atherosclerosis, left ventricular hypertrophy, and diabetes mellitus.[7] Arterial wall stiffness can be noninvasively assessed by measuring pulse wave velocity (PWV) along the aortoiliac pathway.[8] PWV is positively related to wall stiffness; a greater arterial PWV indicates a greater degree of arterial wall stiffness, a characteristic of atherosclerosis.[9] Recently, Sidhu et al[10] reported that rosiglitazone reduced common carotid IMT progression in nondiabetic coronary artery disease patients. Marx et al[11] reported that rosiglitazone has anti-inflammatory and potential antiatherogenic effects including metalloproteinase-9 and IMT reductions. Stakos et al[12] reported that long-term administration of troglitazone to nondiabetic patients with insulin resistance was associated with a decrease in the elastic properties of the aorta, suggesting a negative outcome for arterial elasticity in patients treated with troglitazone. Koshiyama et al[13] reported that pioglitazone decreased IMT in patients with type 2 diabetes. However, little is known about the effects of sulfonylurea and voglibose on UAE, IMT, and PWV in diabetes patients with normal blood pressure and microalbuminuria. We hypothesized that only pioglitazone among antidiabetic drugs can reduce UAE, IMT, and PWV in diabetes patients with nephropathy. The aim of the present study was to compare the effects of pioglitazone (amelioration of insulin resistance), sulfonylurea (augmentation of insulin supply), and voglibose (limitation of postprandial hyperglycemia) on UAE, IMT, and PWV in normotensive diabetes patients with microalbuminuria.

SUBJECTS AND METHODS

Study subjects included 45 patients with type 2 diabetes and microalbuminuria (25 men and 20 women; mean age, 55.5 ± 11.5 years) and 30 healthy controls, including staff in our hospitals (16 men and 14 women; mean age, 54.5 ± 10.8 years). Blood pressure of all the subjects was less than 140/90 mm Hg. Healthy controls had normal serum lipid profiles and had not received any medications. The selection criteria for patients were as follows: (1) no history of ketoacidosis, (2) treatment by diet alone, (3) fasting C-peptide level more than 0.33 mmol/L, and (4) hemoglobin A_{1c} level more than 6.5%.[13] None of the patients showed serum creatinine in excess of 1.5 mg/dL at the time of the study. None of the patients had been given antihypertensive drugs, including angiotensin-converting enzyme inhibitors. There was no malignancy, heart disease, cerebrovascular disease, liver disease, or collagen disease based on physical examinations, urine and blood examination, and radiography, electrocardiography, ultrasound cardiography, or x-ray computed tomography scan data. Patients with he-

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Submitted February 7, 2004; accepted May 4, 2004.

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0026-0495/04/5310-0047$30.00/0
doi:10.1016/j.metabol.2004.05.013

maturia or casturia and those with a known history of nondiabetic renal disease were excluded. This study was preapproved by our human research ethics committees. Informed consent was obtained from each participant. After an overnight fast, blood was drawn from the antecubital vein for measurement of glucose, hemoglobin A_{1c}, serum creatinine, and blood urea nitrogen in all subjects. UAE was estimated from urine volume measured at timed intervals and its albumin concentration measured by radioimmunoassay. The median UAE was based on at least 3 consecutive 4-hour urine collections (at the same time on each occasion on different days).[4] Microalbuminuria was defined as a median UAE of 20 to 200 μg/min. The patients were randomly assigned to 1 of 3 treatment groups by sealed envelop method: treatment with pioglitazone 30 mg/d (n = 15), treatment with glibenclamide 5 mg/d (n = 15), or treatment with voglibose 0.6 mg/d (n = 15). Treatment continued for 12 months. There were no dropouts throughout the study period. In this study, we chose glibenclamide and voglibose as compared controls. Voglibose and glibenclamide are commonly used in diabetes patients.[14-16]

UAE, IMT, and PWV were determined at baseline, 6, and 12 months of treatment. PWV was determined by pulse pressure analyzer (BP-203RPE; Nihon Colin, Tokyo, Japan). Pulse waves were recorded via sensors placed on both posterior tibial arteries. The times required for the pulse waves to travel from the heart to both posterior tibial arteries were determined, and the distances between the heart and both posterior tibial arteries were estimated from the patient's height. The best 10 consecutive pulses were analyzed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing the distance by the travel time.[9] PWV was expressed in centimeters per second. The coefficient of variation was less than 5%. High resolution B-mode ultrasound examination was performed with a 7.5 MHz transducer on the Aloka SSD-2000 scanner (Aloka, Tokyo, Japan). Carotid IMT was measured at points 20, 25, and 30 mm proximal to the flow divider on the far wall of the right and left common carotid arteries at the end of the diastolic phase, and mean IMT was determined for each patient.[17] The coefficient of variation of IMT was 3.5% to 4.5% for repeated scans.

Data are expressed as mean ± SD. All data were normally distributed to justify the use of mean ± SD and *t* testing. Statistical analysis was performed with paired or unpaired Student's *t* test or 1-way analysis of variance followed by Bonferroni testing for multiple comparisons. A *P* value of less than .05 was considered statistically significant.

Table 1. Pretreatment Clinical Data for Type 2 Diabetic Patients per Study Group

	Pioglitazone (n = 15)	Glibenclamide (n = 15)	Voglibose (n = 15)
Age (yr)	56.5 ± 12.0	55.0 ± 11.5	55.0 ± 11.0
Sex (male/female)	9/6	8/7	8/7
Diabetes duration (yr)	17.5 ± 4.5	17.0 ± 4.8	16.8 ± 5.0
Hemoglobin A_{1c} (%)	7.9 ± 1.3	7.8 ± 1.4	8.1 ± 1.6
Serum creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.3	0.9 ± 0.3
Blood urea nitrogen (mg/dL)	18.4 ± 4.8	19.2 ± 3.8	19.6 ± 5.0
Blood pressure (mm Hg)			
Systolic	124 ± 12	120 ± 13	122 ± 12
Diastolic	74 ± 8	78 ± 5	76 ± 6

NOTE. Data are expressed as mean ± SD. All data are not significantly different between groups.

Table 2. Changes in HbA_{1C} (%) Before and After Treatments per Study Group

	Before	6 Months	12 Months
Pioglitazone (n = 15)	7.9 ± 1.3	6.8 ± 1.2*	6.2 ± 1.0†
Glibenclamide (n = 15)	7.8 ± 1.4	6.7 ± 1.3*	6.3 ± 1.1†
Voglibose (n = 15)	8.1 ± 1.6	6.9 ± 1.3*	6.4 ± 1.2†

NOTE. Data are expressed as mean ± SD. HbA_{1C} levels were not different between groups at before, 6 months, and 12 months after treatment.

*$P < .05$ before treatment *v* 6 months after treatment.

†$P < .05$ before treatment *v* 12 months after treatment.

RESULTS

Before treatment, hemoglobin A_{1c}, serum creatinine and blood urea nitrogen, disease duration, and blood pressure differed little between the 3 treatment groups (Table 1). After treatment, hemoglobin A_{1c} was reduced to almost the same degree in all 3 groups (*v* before treatment, $P < .05$). Changes in hemoglobin A_{1c} before treatment and 6 and 12 months after treatment are shown in Table 2. These 3 drugs did not affect serum creatinine, blood urea nitrogen, or blood pressure.

UAE was significantly greater in the 45 diabetes patients (132.5 ± 36.4 μg/min) than in 30 healthy controls (6.2 ± 1.8 μg/min) ($P < .001$). IMT was significantly greater in the diabetes patients (0.76 ± 0.12 mm) than in the controls (0.60 ± 0.08 mm, $P < .01$), and PWV was also significantly greater in the diabetes patients (1,840 ± 320 cm/s) than in the controls (1,350 ± 225 cm/s, $P < .01$) (Fig 1). Before treatment, UAE, IMT, and PWV differed very little between the 3 treatment groups. The changes in UAE before and after treatment are shown in Fig 2. After 6 months, UAE in the pioglitazone group (86.5 ± 24.5 μg/min) was significantly lower than that in the glibenclamide group (142.5 ± 42.5 μg/min, $P < .05$) and voglibose group (143.5 ± 41.5 μg/min, $P < .05$). After 12 months, UAE in the pioglitazone group (44.5 ± 16.4 μg/min) was significantly lower than that in the glibenclamide group (146.8 ± 38.5 μg/min, $P < .01$) and voglibose group (144.8 ± 42.5 μg/min, $P < .01$). The changes in IMT before and after treatment are shown in Fig 3. After 6 and 12 months, IMT in the pioglitazone group (6 months: 0.72 ± 0.13 mm; 12 months: 0.68 ± 0.09 mm) was significantly lower than that in the glibenclamide group (6 months: 0.78 ± 0.10 mm; 12 months: 0.78 ± 0.09 mm, $P < .05$) and voglibose group (6 months: 0.77 ± 0.11 mm; 12 months: 0.77 ± 0.12 mm, $P < .05$). IMT changed little after treatment in the glibenclamide and voglibose groups. The changes in PWV before and after treatment are shown in Fig 4. After 6 and 12 months, PWV was significantly lower in the pioglitazone group (6 months: 1,737 ± 270 cm/s; 12 months: 1,650 ± 250 cm/s) than in the glibenclamide group (6 months: 1,840 ± 210 cm/s; 12 months: 1,850 ± 250 cm/s, $P < .05$) and voglibose group (6 months: 1,850 ± 230 cm/s; 12 months: 1,870 ± 240 cm/s, $P < .05$). PWV changed little after treatments in the glibenclamide and voglibose groups. In the diabetes patients, UAE correlated with IMT ($r^2 = 0.30$, $P < .001$) and PWV ($r^2 = 0.37$, $P < .001$).

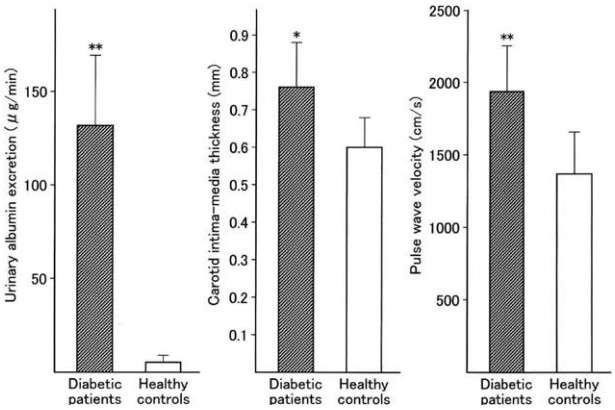

Fig 1. UAE, carotid IMT, and PWV in the 45 diabetic patients and the 30 healthy controls. Diabetic patients *v* healthy controls, *$P < .01$ and **$P < .001$.

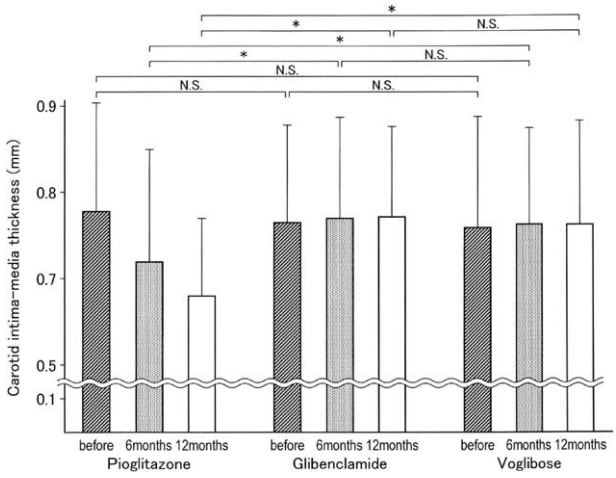

Fig 3. Carotid IMT before treatment and at 6 and 12 months after treatment. *$P < .05$.

DISCUSSION

There has been increasing evidence that thiazolidinediones, including pioglitazone, cause an inhibition of early atherosclerotic process by peroxisome proliferator-activated receptor γ (PPARγ) activation,[18] and that these drugs have a potential beneficial effect on the treatment or prevention of renal and vascular complications of type 2 diabetes.[6] Recent evidence suggests that PPARs exert their anti-inflammatory activities in vascular and immunologic cell types, such as endothelial cells, vascular smooth muscle cells, and monocyte/macrophages. PPAR agonists, such as pioglitazone, have emerged as a potential tool to modulate the inception and progression of atherosclerosis at the level of the arterial wall.[19] We reported previously that pioglitazone is effective for reducing UAE and ameliorating glomerular podocyte injury in early-stage diabetic nephropathy.[20] However, little is known about the effects of other antidiabetic agents, including glibenclamide and voglibose, on UAE, IMT, and PWV. In this study, we first reported that only pioglitazone may have renoprotection and antiatherogenic actions in type 2 diabetes patients with early-stage nephropathy.

Carotid artery IMT is a well-known indicator of atherosclerosis, and IMT abnormalities are prognostic factors in cases of cardiovascular diseases. Raso et al[7] reported IMT of the common carotid arteries to be increased in the presence of coronary artery disease and increased with the number of involved coronary vessels. Some investigators have reported patients with chronic renal failure or diabetes to have a significantly increased carotid artery IMT.[21,22] Increased arterial stiffness, as assessed by PWV, predicts all-cause and cardiovascular mortality in patients with different kinds of disease, including end-stage renal disease and diabetes.[9] Yamashita et al[23] reported PWV to be significantly greater in patients with coronary artery disease than in patients without coronary artery disease, but with hypertension, diabetes, or dyslipidemia. Komai et al[24] reported that PWV may be useful for managing patients with hypertension. Koshiyama et al[13] reported that

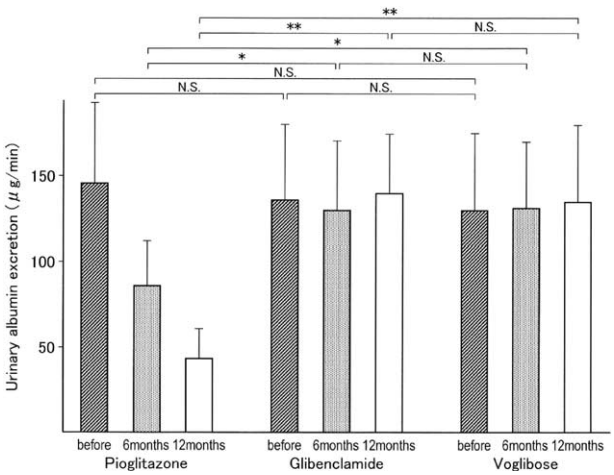

Fig 2. UAE before treatment and at 6 and 12 months after treatment. *$P < .05$ and **$P < .01$.

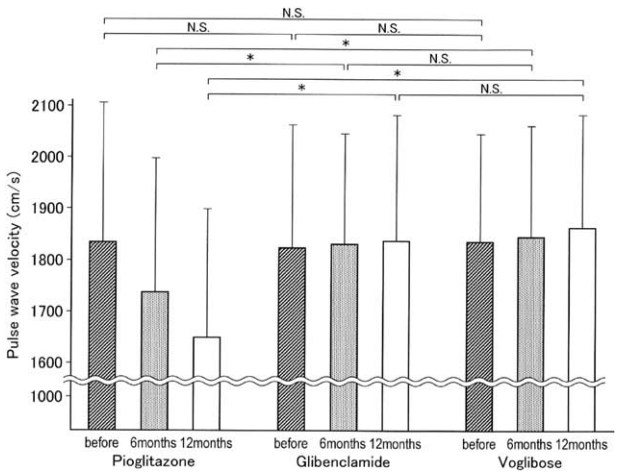

Fig 4. PWV before treatment and at 6 and 12 months after treatment. *$P < .05$.

pioglitazone (30 mg/d) showed a significant decrease in IMT as early as 3 months, and the decrease was also found after 6 months. We reported in the present study that pioglitazone reduces carotid artery IMT and PWV and that neither glibenclamide nor voglibose reduces these markers. Recently, Mahmud et al[25] reported that angiotensin receptor antagonists reduce arterial stiffness in hypertension comparable to and possibly additive to the inhibition achieved by angiotensin-converting enzyme inhibitors. Ludwig et al[26] conducted a double-blind, randomized, controlled study and reported that losartan and atenolol produced comparable reductions in IMT over 24 months in patients with hypertension. The present study involved normotensive diabetes patients not taking antihypertensive drugs. Further studies are needed to clarify the effects of angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors on IMT and PWV in normotensive diabetes patients with microalbuminuria. In the present study, we showed that the changes in carotid IMT in the pioglitazone group are about 0.05 mm at 6 months and 0.09 mm at 12 months compared with baseline. Koshiyama et al[13] reported that the changes in carotid IMT in the pioglitazone group are 0.08 mm at 6 months. However, these data in the statin treatment groups are variable. Taylor et al[27] (United States) reported that the changes in IMT with atrovastatin in patients with hyperlipidemia are about 0.03 mm at 12 months. Youssef et al[28] (United Kingdom) reported that the changes with atrovastatin in patients with hyperlipidemia are about 0.15 mm at 8 weeks. Nolting et al[29] (The Netherlands) reported that the changes with simvastatin in patients with hyperlipidemia are about 0.08 mm at 24 months. This may be due, in part, to the differences in race, primary disease, or drug.

Microalbuminuria usually indicates the beginning of diabetic nephropathy as opposed to overt nephropathy characterized by clinical proteinuria.[30] Microalbuminuria can be considered an early sign of injury not only of the kidneys, but also of the cardiovascular system.[31] We previously reported that pioglitazone, but not glibenclamide or voglibose, reduced UAE in type 2 diabetes patients with microalbuminuria, and that pioglitazone may be useful in the treatment of diabetic nephropathy. Agewall et al[32] reported significant association between UAE and IMT of the common carotid in a group of hypertensive men with maturity-onset diabetes; the association was not found in a large group of nondiabetic hypertensives. However, Pedrinelli et al[33] reported dissociation between UAE and carotid artery IMT in hypertensive men. The pathophysiologic background of microalbuminuria in hypertensive patients may differ from that in diabetes patients. Insulin per se has been suggested to increase the rate of transcapillary albumin escape in nondiabetic men, and there are several studies reporting a relationship between insulin sensitivity and UAE in different populations.[34,35] In the present study, we observed a significant association between UAE and carotid artery IMT in normotensive diabetes patients.

In summary, pioglitazone, not glibenclamide or voglibose, reduced UAE, carotid artery IMT, and PWV in type 2 diabetes patients with microalbuminuria, suggesting that pioglitazone may be useful in the amelioration of endothelial dysfunction and atherosclerosis.

ACKNOWLEDGMENT

We thank Natsuko Yoneda, Takeda Chemical Industries, Osaka, Japan, for her helpful suggestions. We also thank Yoshinobu Takahashi, Shinmatsudo Central General Hospital, for his technical assistance.

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