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Long-term pioglitazone therapy improves arterial stiffness in patients with type 2 diabetes mellitus

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Abstract

Pioglitazone, a peroxisome proliferator–activated receptor γ agonist, not only improves insulin resistance and glycemic control, but may also have additional beneficial vascular effects in patients with type 2 diabetes mellitus. We investigated whether pioglitazone had an influence on arterial stiffness, which is an independent predictor of cardiovascular events, in 204 patients with type 2 diabetes mellitus. A prospective, nonrandomized, open-label trial was performed that involved 41 patients treated with pioglitazone, 46 patients receiving sulfonylureas, 67 patients on insulin, and 50 patients on diet/exercise only. The follow-up period was 56 ± 3 months. Arterial stiffness was evaluated by using the arterial stiffness index (ASI), which was based on analysis of the pulse wave amplitude pattern obtained during automated blood pressure measurement in the upper limb. The 4 groups had a similar baseline ASI, which was greater than the reference range in each group. Although antidiabetic therapies improved hemoglobin A_{1c} and low-density lipoprotein cholesterol, ASI only decreased significantly in the pioglitazone group. Thus, pioglitazone improved abnormal arterial stiffness in patients with type 2 diabetes mellitus via a mechanism beyond the metabolic improvement. These findings may have important clinical implications in the use of pioglitazone in patients with type 2 diabetes mellitus.

1. Introduction

Patients with type 2 diabetes mellitus have a high risk of developing both microvascular and macrovascular disease, showing a 2- to 4-fold increase of coronary heart disease compared with the general population [1,2]. Intensive glycemic control is able to reduce microvascular complications, but its effect on macrovascular changes and cardiovascular disease is rather limited [3]. The United Kingdom Prospective Diabetes Study demonstrated that the risk of cardiovascular morbidity and mortality was reduced in patients with type 2 diabetes mellitus receiving metformin [4], which improves insulin sensitivity, and also showed the importance of managing the traditional cardiovascular risk factors, such as a high hemoglobin (Hb) A_{1c} level, dyslipidemia, hypertension, and central obesity, all of which are associated with insulin resistance [5]. Recently, the peroxisome proliferator–activated receptor γ (PPARγ) agonist pioglitazone has been widely used as an insulin sensitizer to treat insulin resistance and type 2 diabetes mellitus [6,7]. The Prospective Pioglitazone Clinical Trial in Macrovascular Events study revealed that pioglitazone significantly reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes mellitus, and treatment with this drug led to a significant (16%) reduction in the risk of the main end point (cardiovascular death or nonfatal myocardial infarction) [8,9].

Several studies have shown that an increase of blood pressure and pulse pressure is a major risk factor for myocardial infarction [10,11], stroke [12], and cardiovascular death in the general population [13] and is also associated with increased insulin resistance [14]. Most epidemiologic studies have demonstrated that increased arterial stiffness (a major determinant of the pulse pressure) is an independent predictor of cardiovascular morbidity and

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mortality [10-13]. Arterial stiffness has been assessed by measurement of the pulse wave velocity (PWV) between the carotid and femoral arteries [12,13] or by measuring the brachial-ankle PWV [15]. More recently, several noninvasive and reproducible methods have been developed for measuring arterial stiffness. The arterial stiffness index (ASI) is a useful indicator of brachial artery stiffness that can be obtained simultaneously with automated measurement of the blood pressure in the upper limb by computer-assisted oscillometry [16]. The ASI has been reported to show a good correlation with the carotid-femoral PWV and is considered to be a valuable indicator of arterial stiffness in hypertensive patients with or without type 2 diabetes mellitus or dyslipidemia [15,17,18]. In a previous population-based study, we found that the ASI increased along with an increase in the number of traditional cardiovascular risk factors [19]. Because only a few minutes are needed for measurement of the ASI, it can be assessed repeatedly in outpatients over the long term.

In the present study, we investigated the influence of long-term pioglitazone therapy on arterial stiffness (the ASI) in patients with type 2 diabetes mellitus and compared the results with those for patients receiving other antidiabetic therapies.

2. Patients and methods

2.1. Patients

A total of 204 outpatients with type 2 diabetes mellitus (118 men and 86 women) were enrolled in the present study after giving informed consent. Their ages ranged from 30 to 85 years (63 ± 11 years, mean ± SD). Type 2 diabetes mellitus was defined according to the Japan Diabetes Society criteria. Patients with any of the following macrovascular or microvascular diseases were excluded: myocardial infarction, cerebrovascular disease, heart failure, severe liver dysfunction, renal failure, and diabetic retinopathy.

The study was designed as a prospective, nonrandomized, open-label trial. All of the subjects were diagnosed with type 2 diabetes mellitus (n = 204) and were initially entered into a diet and exercise therapy for several months of observation. Afterward, the patients were classified into 4 groups based on their diabetic conditions. Patients who responded to the diet/exercise therapy were assigned to the diet and exercise group (n = 50). Patients with poor blood glucose control during the diet/exercise therapy received treatment with a sulfonylurea, pioglitazone, or insulin in addition to the diet/exercise therapy depending on their diabetic profile. Patients with marked insulin resistance or poor insulin secretion received pioglitazone or insulin, respectively. Patients who responded to a sulfonylurea continued such treatment throughout the study and were assigned to the sulfonylurea group (n = 46). Patients with little response to sulfonylurea therapy received pioglitazone in addition to the sulfonylurea or switched to insulin. Patients who required insulin therapy or received pioglitazone, after initial diet/exercise therapy or after sulfonylurea therapy, were assigned to the insulin group (n = 67) or the pioglitazone group (n = 41), respectively. Pioglitazone was started at a dose of 7.5 mg or 15 mg daily and then was titrated to 30 mg, depending on tolerability. All drug-treated patients continued their diet and exercise therapy.

2.2. Measurement of biochemical parameters

All patients fasted for more than 9 hours before blood collection. After resting for 5 minutes, the blood pressure (systolic and diastolic) and pulse rate were measured and recorded. Afterward, 10 mL of blood was collected from the median antecubital vein into a plain tube for biochemistry tests. All parameters were measured using an autoanalyzer (JCA-BM8060; Jeol, Japan).

2.3. Measurement of the ASI

The ASI was measured in all patients using a CardioVision (MS-2000; IMDP, Las Vegas, NV). The device occludes the brachial artery by increasing cuff pressure until it exceeds the systolic blood pressure. After occluding the artery, the cuff slowly deflates automatically; and a pressure sensor attached to the cuff measures small volumetric changes caused by the pulse wave, which increases in amplitude as blood flow in the brachial artery slowly increases. The amplitude of these volumetric changes becomes maximal when the cuff pressure is near the mean arterial pressure. At this point, the elastic properties of the brachial artery also are maximal. After the pulse wave peak, the amplitude decreases again as the cuff deflates and the brachial artery becomes fully open.

To determine the ASI, the *flat upper part* of the pulse wave pattern was defined as the region between the highest point (100%) and 80% of the amplitude. Afterward, the ASI was calculated as the pressure range (millimeters of mercury × 10) of the oscillometric curve corresponding to the upper 5% of this flat area (Fig. 1).

Arrhythmias influence the pulse wave pattern, so measurements made in the presence of premature beats or atrial fibrillation were excluded.

Measurement of the ASI was repeated 5 times per patient. After excluding the maximum and minimum values from

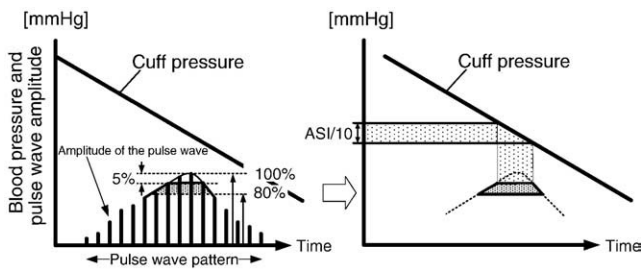

Fig. 1. Relation between the pulse wave pattern and cuff pressure during automated blood pressure measurement. The ASI was calculated by computer-assisted oscillometry as the pressure range (millimeters of mercury × 10) corresponding to the upper 5% of the oscillometric curve.

Table 1
Patient characteristics at baseline

	PIO (n = 41)	SU (n = 46)	Insulin (n = 67)	D & E (n = 50)
Men (n)	28 (68%)	23 (50%)	38 (57%)	29 (58%)
Women (n)	13 (32%)	23 (50%)	29 (43%)	21 (42%)
Age (y)				
°Range	37-79	40-77	30-85	36-85
°Mean ± SD	60 ± 10	63 ± 9	63 ± 13	65 ± 10
Antihypertensive drugs (%)	31*	54	36*	64
Lipid-lowering drugs (%)	12	20	16	22
ASI	108 ± 48	114 ± 56	114 ± 51	113 ± 52
HbA_{1c} (%)	8.1 ± 1.6†	8.3 ± 1.3†	8.7 ± 1.5†	7.0 ± 1.7
Medication period (mo)	56 ± 3	56 ± 3	56 ± 3	56 ± 3

PIO indicates pioglitazone; SU, sulfonylurea; D & E, diet and exercise.
* Significant difference vs diet and exercise ($P < .01$).
† Significant difference vs diet and exercise ($P < .01$).

these 5 measurements, the mean of the remaining 3 values was calculated as the representative value for each patient.

2.4. Statistical analysis

Data are expressed as the mean ± standard deviation (SD). When comparing mean values between 2 groups or multiple groups, we used the unpaired *t* test and the Bonferroni/Dunn test, respectively. The effects of medications on each clinical parameter were assessed by the paired *t* test and Pearson linear correlation analysis. The χ^2 test was performed for comparisons between the groups. If the distribution of a parameter was not normal, Wilcoxon signed rank test was used. In all analyses, a *P* value of less than .05 was considered significant.

3. Results

At baseline, the patients in each group were comparable with respect to sex ratio, age, use of lipid-lowering drugs (statins), and duration of medication (Table 1). There were also no significant differences of the ASI between the groups, and it was significantly elevated in all 4 groups compared with the reference range (from 20 to 70).

In the diet and exercise group, treatment with antihypertensive drugs (calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) was significantly more common than in the pioglitazone group and the insulin group. Patients in the diet and exercise group had significantly lower HbA_{1c} levels compared with those in the other groups.

The blood pressure and parameters of glucose and lipid metabolism were also comparable between the 4 groups at baseline (Table 2).

3.1. Influence of pioglitazone and sulfonylureas on ASI

In the pioglitazone group, the baseline ASI was 108 ± 48; and there was no significant change by the start of treatment with pioglitazone after 16 ± 6 months (ASI = 104 ± 51). However, at the end point of the study (after 39 ± 6 months of

Table 2
Effect of each treatment on variables

		Pioglitazone	Sulfonylurea	Insulin	Diet/Exercise
SBP	baseline	155 ± 19	158 ± 2	152 ± 20	157 ± 17
	start or 1 year	147 ± 18	152 ± 181	150 ± 22	155 ± 17
	end (56±3)	140 ± 14	150 ± 21	145 ± 21	148 ± 19
DBP	baseline	83 ± 12	82 ± 10	78 ± 12	82 ± 12
	start or 1 year	79 ± 12	80 ± 10	75 ± 12	80 ± 11
	end (56±3)	78 ± 10	81 ± 19	77 ± 12	79 ± 12
FBG	baseline	176 ± 51	189 ± 54	229 ± 70	147 ± 57
	start or 1 year	174 ± 46	163 ± 37	220 ± 59	152 ± 52
	end (56±3)	157 ± 34	184 ± 56	221 ± 76	148 ± 61
TG	baseline	203 ± 272	180 ± 93	171 ± 90	188 ± 120
	start or 1 year	154 ± 97	170 ± 95	140 ± 78	158 ± 103
	end (56±3)	134 ± 65	162 ± 88	151 ± 88	151 ± 79
T-cho	baseline	217 ± 32	227 ± 44	216 ± 34	218 ± 40
	start or 1 year	212 ± 34	219 ± 44	208 ± 35	213 ± 33
	end (56±3)	207 ± 35	217 ± 42	207 ± 46	207 ± 36
HDL-c	baseline	56 ± 16	69 ± 57	65 ± 29	60 ± 21
	start or 1 year	55 ± 12	62 ± 32	58 ± 15	58 ± 18
	end (56±3)	58 ± 14	56 ± 16	61 ± 20	56 ± 20
LDL-c	baseline	139 ± 29	145 ± 39	134 ± 38	136 ± 41
	start or 1 year	132 ± 27	135 ± 40	129 ± 34	130 ± 37
	end (56±3)	122 ± 30	127 ± 35	116 ± 36	119 ± 34

SBP indicates systolic blood pressure (millimeters of mercury); DBP, diastolic blood pressure (millimeters of mercury); FBG, fasting blood glucose (milligrams per deciliter); TG, triglycerides (milligrams per deciliter); T-cho, total cholesterol (milligrams per deciliter); HDL-c, HDL cholesterol (milligrams per deciliter); LDL-c, LDL cholesterol (milligrams per deciliter).
*$P < .05$, **$P < .01$.

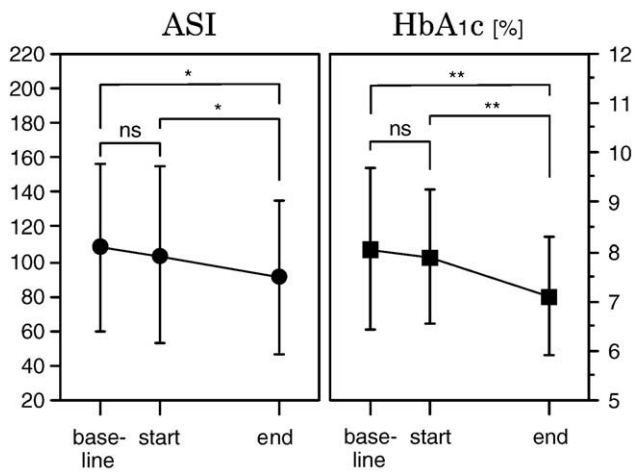

Fig. 2. Changes of the ASI and HbA_{1c} in the pioglitazone group. There were no significant changes between measurements obtained just before starting diet and exercise therapy (baseline) and the start of pioglitazone treatment (start). However, both ASI and HbA_{1c} were significantly improved by pioglitazone treatment at the study end point (end). Bars represent the mean ± SD. *$P < .05$, **$P < .01$. NS indicates not significant.

pioglitazone treatment), the ASI was significantly reduced to 91 ± 44 ($P < .05$) (Fig. 2). A beneficial effect of pioglitazone therapy on HbA_{1c} was also observed at the study end point (7.1% ± 1.2%) compared with the values at baseline (8.1% ± 1.6%, $P < .01$) or at the start of pioglitazone treatment (7.9% ± 1.4%, $P < .01$).

In the sulfonylurea group, HbA_{1c} was also significantly lower at the study end point (7.5% ± 1.3%) compared with the value at baseline (8.3% ± 1.3%) or at the start of sulfonylurea treatment (8.2% ± 1.3%). Despite this, no significant change of ASI occurred during the study because it was 114 ± 56 at baseline, 105 ± 60 at the start of sulfonylurea treatment, and 111 ± 58 at the study end point (Fig. 3).

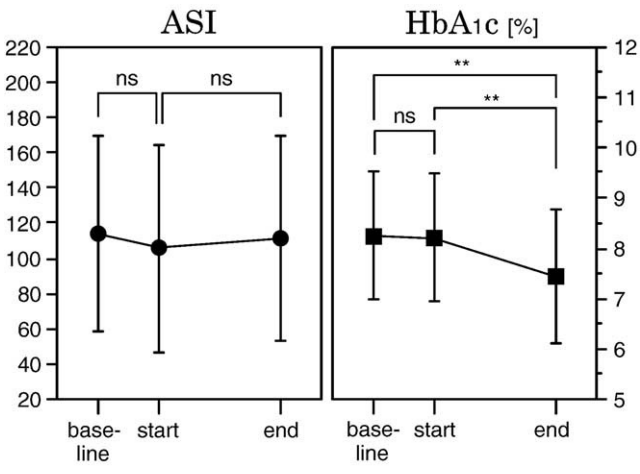

Fig. 3. Changes of the ASI and HbA_{1c} in the sulfonylurea group. A significant improvement of HbA_{1c} was observed after sulfonylurea treatment, but there was no improvement of ASI. Bars represent the mean ± SD. **$P < .01$.

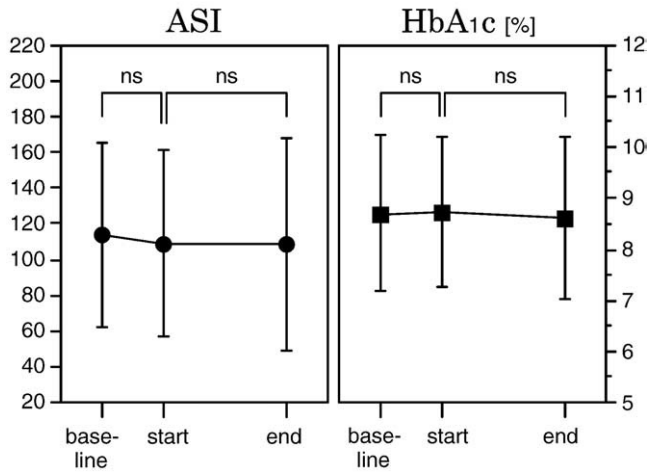

Fig. 4. Influence of insulin on the ASI and HbA_{1c}. Bars represent the mean ± SD.

3.2. Influence of insulin on ASI

Patients assigned to the insulin group showed a poor response to diet and exercise and/or sulfonylurea treatment. They had a similar HbA_{1c} level at baseline (8.7% ± 1.5%), at the start of treatment (8.7% ± 1.5%), and at the study end point (8.6% ± 1.6%). There was also little change of ASI at the study end point (109 ± 60) compared with that at baseline (114 ± 51) and at the start of insulin treatment (109 ± 53) (Fig. 4).

3.3. Influence of diet and exercise on ASI

Patients assigned to the diet and exercise group were considered to have mild to moderate diabetes because they did not need antidiabetic agents, and the baseline HbA_{1c} level of this group was significantly lower (7.0 ± 1.7, $P < .01$) than that of the other 3 groups (Table 1). After initiation of the diet and exercise regimen, HbA_{1c} showed a significant

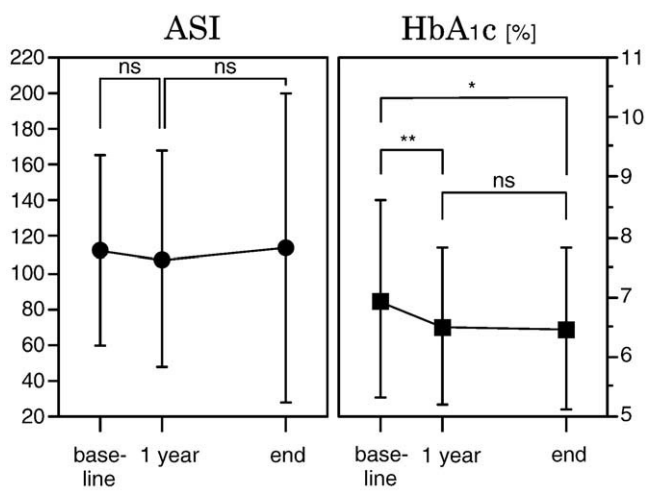

Fig. 5. Changes of the ASI and HbA1c in the diet and exercise group. Although HbA_{1c} improved, ASI showed no significant change. Bars represent the mean ± SD. *$P < .05$, **$P < .01$.

reduction to 6.5% ± 1.3% ($P < .01$) at 1 year; and the improvement persisted throughout the study (6.5% ± 1.3% at the study end point). Despite the improvement of HbA_{1c}, the ASI was high at baseline (113 ± 52), similar to that in the other 3 groups; remained high after 1 year (108 ± 60); and was still elevated at the study end point (114 ± 85) (Fig. 5).

3.4. Changes of lipid metabolism and blood pressure

With each medication, there was a marked decrease of low-density lipoprotein (LDL) cholesterol; and a significant reduction was seen by the study end point. However, high-density lipoprotein (HDL) cholesterol only increased in the pioglitazone group. In addition to these changes of the lipid profile, the systolic and diastolic blood pressure also improved in all groups (Table 2).

4. Discussion

The Prospective Pioglitazone Clinical Trial in Macrovascular Events study has shown that treatment of type 2 diabetes mellitus with pioglitazone could reduce cardiovascular morbidity and mortality [8,9]. In the present long-term study, we demonstrated that treatment with pioglitazone for an average of 39 months improved arterial stiffness, an important indicator of the risk of cardiovascular events, along with a decrease of HbA_{1c} and LDL cholesterol. Accordingly, pioglitazone treatment may have a preventive effect on atherosclerosis in patients with type 2 diabetes mellitus. To our knowledge, this is the first study to show that long-term treatment with a PPARγ agonist can improve atherogenic changes in Japanese patients with type 2 diabetes mellitus.

Although glycemic control did not differ between the pioglitazone group and the sulfonylurea group (based on HbA_{1c} values), the ASI only showed a significant decrease in the pioglitazone group. There is both in vitro and in vivo evidence that pioglitazone has antiatherogenic effects unrelated to its improvement of glycemic control, which are primarily mediated through a direct action on the vasculature [6,7]. Despite the existence of such experimental data, whether pioglitazone actually has a direct antiatherogenic effect independent of its antidiabetic activity in patients with type 2 diabetes mellitus has not been fully clarified. In recent years, it has become apparent that control of high blood pressure and LDL cholesterol can substantially reduce the cardiovascular risk of diabetic patients [14]. Therefore, it seems possible that the antiatherogenic effect of pioglitazone on arterial stiffness was mediated through its influence on lipid metabolism, including reduction of LDL cholesterol, elevation of HDL cholesterol, and reduction of triglycerides [6,7]. The present study showed that LDL cholesterol levels were significantly decreased in both the pioglitazone group and the sulfonylurea group, without any significant changes of triglyceride levels. In the pioglitazone group, however, HDL cholesterol also increased significantly. Accordingly, the antiatherogenic effect of pioglitazone might not be mediated so much through changes of the lipid profile or may possibly be related to the increase of HDL cholesterol.

To treat hypertension, another major cardiovascular risk of diabetic patients, could be effective to prevent atherogenic changes in the arteries [14]. The various antihypertensive drugs have been shown to reduce arterial stiffness in patients with essential hypertension. In the present study, the beneficial effects of antihypertensive drugs on arterial stiffness were not evident in the diet and exercise group, in which there were a significantly larger number of patients on antihypertensive drugs compared with the pioglitazone group. This suggests that antiatherogenic effects of pioglitazone might be independent of antihypertensive therapies.

The antiatherogenic effects of pioglitazone in patients with type 2 diabetes mellitus have already been studied in relatively short-term clinical trials and were evaluated by using various markers, such as the PWV [20,21], stiffness parameter β [22], carotid intima-media thickness [21,23-26], inflammatory markers (C-reactive protein and high-sensitivity C-reactive protein) [20,27], and hormones like leptin or adiponectin [20,22]. Previous evidence taken together with our data suggest that pioglitazone could be useful for preventing macrovascular complications in patients with type 2 diabetes mellitus via a direct influence on the vasculature and also through its modulation of glucose and lipid metabolism.

Arterial stiffness is influenced by changes of arterial wall structure, including accumulation of collagen and smooth muscle cell proliferation; by functional alterations such as increased vascular tone and endothelial dysfunction; and/or by oxidative and inflammatory stresses [6,7]. We showed that arterial stiffness was reduced by pioglitazone treatment in patients with type 2 diabetes mellitus. It is known that pioglitazone improves insulin resistance and glycemic control, but the mechanisms underlying the vascular effects of this drug are not fully clear. In recent studies, pioglitazone has been demonstrated to improve endothelial dysfunction in diabetic patients as assessed by flow-mediated endothelium-dependent vasodilatation of the brachial artery [25,28,29]. It has been suggested that pioglitazone directly increases nitric oxide release from endothelial cells expressing PPARγ messenger RNA [28]. Pioglitazone also acts directly on vascular smooth muscle cells to attenuate vasoconstriction by inhibiting L-type calcium channels [30]. Recent findings have suggested that insulin resistance in the blood vessels is characterized by both activation of mitogen-activated protein kinase signaling and inhibition of phosphoinositol 3 kinase, whereas it has been shown that pioglitazone inhibits mitogen-activated protein kinase activation and enhances the phosphoinositol 3 kinase pathway [29]. Pioglitazone also has various other vascular effects because it inhibits arterial expression of connective tissue growth factor [31], increases neoangiogenesis [32], reduces vascular wall elastocalcinosis [33], increases superoxide dismutase activity [34], and

suppresses the growth of vascular smooth muscle cells [35,36].

Even with optimal control of hypertension, dyslipidemia, and other conventional cardiovascular risk factors, patients with type 2 diabetes mellitus still display an excess risk of macrovascular disease compared with patients who do not have diabetes. Therefore, new approaches are needed to further reduce the occurrence of cardiovascular events in patients with type 2 diabetes mellitus. Our present findings suggest that long-term pioglitazone therapy could be useful for preventing macrovascular complications due to both the direct vascular effects of this agent and its influence on glucose and lipid metabolism.

References

[1] Schernthaner G. Cardiovascular mortality and morbidity in type 2 diabetes mellitus. Diabetes Res Clin Pract 1996;31(Suppl):S3-S13.

[2] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.

[3] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

[4] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352: 854-65.

[5] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

[6] Mizushige K, Tsuji T, Noma T. Pioglitazone: cardiovascular effects in prediabetic patients. Cardiovasc Drug Rev 2002;20:329-40.

[7] Irons BK, Greene RS, Mazzolini TA, Edwards KL, Sleeper RB. Implications of rosiglitazone and pioglitazone on cardiovascular risk in patients with type 2 diabetes mellitus. Pharmacotherapy 2006;26: 168-81.

[8] Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A, PROactive Study Group. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. Diabetes Care 2004;27: 1647-53.

[9] Wilcox R, Bousser MG, Betteridge DJ, Schernthaner G, Pirags V, Kupfer S, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007; 38:865-73.

[10] Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003;107:2864-9.

[11] Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184-9.

[12] Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236-41.

[13] Amar J, Ruidavets JB, Chamontin B, Drouet L, Ferrieres J. Arterial stiffness and cardiovascular risk factors in a population-based study. J Hypertens 2001;19:381-7.

[14] Ajjan RA, Grant PJ. Cardiovascular disease prevention in patients with type 2 diabetes: the role of oral anti-diabetic agents. Diabetes Vasc Dis Res 2006;3:147-58.

[15] Kaibe M, Ohishi M, Komai N, Ito N, Kasuya T, Rakugi H, et al. Arterial stiffness index: a new evaluation for arterial stiffness in elderly patients with essential hypertension. Geriatr Gerontol Int 2002;2:199-205.

[16] Shimazu H, Kawarada A, Ito H, Yamakoshi K. Electric impedance cuff for the indirect measurement of blood pressure and volume elastic modulus in human limb and finger arteries. Med Biol Eng Comput 1989;27:477-83.

[17] Reiffel JA. Is arterial stiffness a contributing factor to atrial fibrillation in patients with hypertension? A preliminary investigation. Am J Hypertens 2004;17:213-6.

[18] Chappell LT, Angus RC, Stahl JP, Evans R. Brachial artery stiffness testing as an outcomes measurement for EDTA-treated patients with vascular disease. Clin Pract Altern Med 2000;1:225-8.

[19] Sato H, Hayashi J, Harashima K, Shimazu H, Kitamoto K. A population-based study of arterial stiffness index in relation to cardiovascular risk factors. J Atheroscler Thromb 2005;12:175-80.

[20] Satoh N, Ogawa Y, Usui T, Tagami T, Kono S, Uesugi H, et al. Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care 2003;26:2493-9.

[21] Nakamura T, Matsuda T, Kawagoe Y, Ogawa H, Takahashi Y, Sekizuka K, et al. Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism 2004;53:1382-6.

[22] Araki T, Emoto M, Teramura M, Yokoyama H, Mori K, Hatsuda S, et al. Effect of adiponectin on carotid arterial stiffness in type 2 diabetic patients treated with pioglitazone and metformin. Metabolism 2006;55: 996-1001.

[23] Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y. Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. J Clin Endocrinol Metab 2001;86:3452-6.

[24] Park JS, Cho MH, Lee KY, Kim CS, Kim HJ, Nam JS, et al. The effects of pioglitazone on cerebrovascular resistance in patients with type 2 diabetes mellitus. Metabolism 2007;56:1081-6.

[25] Takebayashi K, Suetsugu M, Wakabayashi S, Aso Y, Inukai T. Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. Metabolism 2007;56:451-8.

[26] Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RBS, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296:2572-81.

[27] Wang CH, Ting MK, Verma S, Kuo LT, Yang NI, Hsieh IC, et al. Pioglitazone increases the numbers and improves the functional capacity of endothelial progenitor cells in patients with diabetes mellitus. Am Heart J 2006;152:1051.e1-8.

[28] Martens FM, Visseren FL, de Koning EJ, Rabelink TJ. Short-term pioglitazone treatment improves vascular function irrespective of metabolic changes in patients with type 2 diabetes. J Cardiovasc Pharmacol 2005;46:773-8.

[29] Rudofsky Jr G, Reismann P, Grafe IA, Konrade I, Djuric Z, Tafel J, et al. Improved vascular function upon pioglitazone treatment in type 2 diabetes is not associated with changes in mononuclear NF-kappaB binding activity. Horm Metab Res 2007;39:665-71.

[30] Zhang F, Sowers JR, Ram JL, Standley PR, Peuler JD. Effects of pioglitazone on calcium channels in vascular smooth muscle. Hypertension 1994;24:170-5.

[31] Game BA, He L, Jarido V, Nareika A, Jaffa AA, Lopes-Virella MF, et al. Pioglitazone inhibits connective tissue growth factor expression in advanced atherosclerotic plaques in low-density lipoprotein receptor–deficient mice. Atherosclerosis 2007;192: 85-91.

[32] Gensch C, Clever YP, Werner C, Hanhoun M, Bohm M, Laufs U. The PPAR-gamma agonist pioglitazone increases neoangiogenesis and prevents apoptosis of endothelial progenitor cells. Atherosclerosis 2007;192:67-74.
[33] Gaillard V, Casellas D, Seguin-Devaux C, Schohn H, Dauca M, Atkinson J, et al. Pioglitazone improves aortic wall elasticity in a rat model of elastocalcinotic arteriosclerosis. Hypertension 2005;46:372-9.
[34] Matsumoto T, Noguchi E, Kobayashi T, Kamata K. Mechanisms underlying the chronic pioglitazone treatment-induced improvement in the impaired endothelium-dependent relaxation seen in aortas from diabetic rats. Free Radic Biol Med 2007;42:993-1007.
[35] Igarashi M, Hirata A, Yamaguchi H, Tsuchiya H, Ohnuma H, Tominaga M, et al. Characterization of an inhibitory effect of pioglitazone on balloon-injured vascular smooth muscle cell growth. Metabolism 2001;50:955-62.
[36] Peuler JD, Phare SM, Iannucci AR, Hodorek MJ. Differential inhibitory effects of antidiabetic drugs on arterial smooth muscle cell proliferation. Am J Hypertens 1996;9:188-92.