*Original Article*

# Comparison of the Effects of Pioglitazone and Metformin on Insulin Resistance and Hormonal Markers in Patients with Impaired Glucose Tolerance and Early Diabetes

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**Impaired glucose tolerance (IGT) is associated with cardiovascular risk factors, but the effects of pioglitazone and metformin on IGT are not well described. We tested the hypothesis that each drug would exhibit antiatherogenic and anti-inflammatory effects in subjects with IGT and early diabetes. The study design was a prospective, randomized, open label, cross-over study. Blood tests, including a 75-g oral glucose tolerance test (OGTT), were performed at baseline and after each treatment. Pioglitazone 15 mg/day or metformin 500–750 mg/day was given for 3 months. Biochemical markers to assess insulin resistance as well as lipid, inflammatory, neurohumoral, and hemostatic factors were included. Twenty-five subjects (17 male, 8 female; age [mean±SD]: 61±9 years; 84% hypertensive) completed the protocol. Of 25 subjects, 14 were diagnosed as IGT and 11 as diabetes with 75-g OGTT. Pioglitazone significantly reduced fasting glucose ($p<0.05$), and homeotasis model assessment of insulin resistance (HOMA-IR) ($p<0.05$) and metformin ($p<0.01$) reduced cholesterol. Both drugs significantly reduced aldosterone (both $p<0.05$) and von Willebrand factor (vWF) (both $p<0.05$). Plasma adiponectin was increased only by pioglitazone ($p<0.001$). Neither drug affected BP levels. In conclusion, pioglitazone was superior to metformin for the improvement of insulin resistance and adiponectin, and both drugs were equally effective in reducing vWF and aldosterone in subjects with IGT and early diabetes. Early intervention with pioglitazone or metformin therapy may reduce the incidence of future cardiovascular disease in subjects with impaired glucose tolerance or early diabetes. (*Hypertens Res* 2007; 30: 23–30)**

***Key Words*: pioglitazone, metformin, insulin resistance, von Willebrand factor, aldosterone**

## Introduction

Several epidemiological studies have shown that impaired glucose tolerance (IGT) is a risk factor for cardiovascular disease (*1–4*). In the Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe (DECODE) study, an elevated glucose level after a 2-h 75-g oral glucose tolerance test (OGTT) was associated with cardiovascular mortality. IGT is characterized by a moderately high glucose level (140 mg/dl to 200 mg/dl) after a 2-h OGTT, and shows a clustering of several risk factors linked with cardiovascular events (*1*). In the Framingham study, the prevalence of IGT was 15–17% in hypertensive subjects (*5*). If hypertension coexists with

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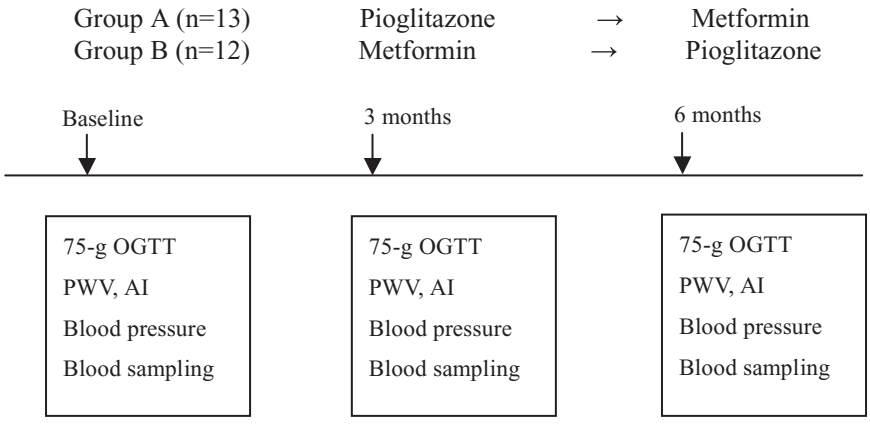


**Fig. 1.** *Study protocol. Each examination was performed 3 times: once at baseline, once after 3 months pioglitazone therapy, and once after 3 months of metformin therapy. The order of each drug was randomly assigned to either group A or group B. OGTT, oral glucose tolerance test; PWV, pulse wave velocity; AI, carotid augmentation index.*

IGT, the risk of coronary heart disease or other cardiovascular events multiplies (*6*). IGT is often under-diagnosed until 75-g OGTT is performed, and it can easily progress to type 2 diabetes or metabolic syndrome (*7*).

Pioglitazone is an antidiabetic drug classified as a peroxisome proliferator–activated receptor-γ agonist, thiazolidinedione. In diabetic subjects, pioglitazone has several beneficial effects not only for lowering plasma glucose but also for improving lipid profile and insulin resistance, and also has anti-atherogenic effects (*8*). In a large clinical trial with diabetic patients, pioglitazone reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke (*9*). On the other hand, there is growing evidence that metformin improves insulin resistance, cardiovascular risk factors, and the development of diabetes mellitus (*10*, *11*). However, no studies have directly compared the effects of pioglitazone and metformin on IGT or early diabetic subjects. We conducted a randomized study to compare the effects of pioglitazone and metformin on insulin sensitivity, inflammatory markers, and atherogenic markers in IGT and early diabetic subjects.

## Methods

### Design and Drugs

This study was a prospective randomized cross-over study using pioglitazone (15 mg/day) and metformin (500–750 mg/day). We randomized the subjects by the order of each drug; group A ($n=13$) was given pioglitazone first and group B ($n=12$) got metformin first. As shown in Fig. 1, the examinations were performed three times: at the baseline and then at 3 months after treatment with each drug. We performed this study at outpatient clinics of Jichi Medical University School of Medicine Hospital and Shioya General Hospital in Tochigi, Japan, from April 2004 to August 2005. This study was approved by the regional Ethics Committee of each hospital. Written informed consent was obtained from all patients beforehand. The dosages approved by the Japanese Ministry of Health, Labor, and Welfare are 500–750 mg for metformin and 15–45 mg for pioglitazone.

### Subjects

Initially, 31 subjects who were diagnosed as IGT with 75-g OGTT or as suspected IGT with fasting glucose were enrolled in this study. IGT was diagnosed according to the WHO criteria: fasting plasma glucose (FPG) ≥110 mg/dl and <126 mg/dl, and 2-h plasma glucose levels after 75-g OGTT ≥140 mg/dl and <200 mg/dl (*12*). We included 5 subjects with FPG ≥126 mg/dl and 6 subjects with 2-h post-OGTT glucose ≥200 mg/dl who were incidentally diagnosed as diabetes but whose hemoglobin A1c was <6.3% and who had never been treated for diabetes or had diabetic symptoms. Thus we defined these subjects as having early diabetes. We excluded patients with renal failure (serum creatinine >1.5 mg/dl), hepatic damage, ischemic heart disease or other cardiac diseases, congestive heart failure, arrhythmias (including atrial fibrillation and other arrhythmias), stroke (including transient ischemic attacks), or other concomitant diseases. Hypertension was defined either by a previously established diagnosis or by an average clinical systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP of ≥90 mmHg (average for each patient on two or more occasions).

### Measures

Smoking was defined as current smoking, and drinking was defined as a current drinking habit. Hyperlipidemia was defined as either total cholesterol >240 mg/dl or the current taking of antihyperlipidemic drugs. Regular exercise was defined as exercising regularly. Body mass index was calcu-

**Table 1. Baseline Characteristics of the Patients**

| Variables | Group A ($n$=13) | GroupB ($n$=12) |
|---|---|---|
| Age (years) | 61±7 | 61±11 |
| Male sex (%) | 54 | 83 |
| Height (m) | 1.6±0.1 | 1.6±0.1 |
| Weight (kg) | 63±10 | 69±10 |
| Body mass index (kg/m$^2$) | 25±3 | 26±3 |
| Waist circumference (cm) | 85±9 | 89±6 |
| Hip circumference (cm) | 95±7 | 95±6 |
| Hypertension (%) | 85 | 83 |
| Hyperertension history (years) | 13±10 | 9±11 |
| Smoking (%) | 23 | 25 |
| Drinking (%) | 46 | 58 |
| Hyperlipidemia (%) | 31 | 50 |
| Hemoglobin A1c (%) | 5.8±0.4 | 5.5±0.2 |
| Regular exercise (%) | 31 | 67 |
| Systolic BP (mmHg) | 149±18 | 143±19 |
| Diastolic BP (mmHg) | 84±13 | 73±22 |
| Pulse rate (bpm) | 73±12 | 80±14 |
| Calcium channel blockers (%) | 38 | 50 |
| AII receptor blockers (%) | 46 | 42 |
| ACE inhibitors (%) | 8 | 0 |
| Diuretics (%) | 23 | 25 |
| $\alpha_1$-Blockers (%) | 15 | 8 |
| β-Blockers (%) | 8 | 8 |
| Statins (%) | 8 | 33 |
| Others (%) | 0 | 8 |

Data are shown as mean±SD or percentages. BP, blood pressure; AII, angiotensin II; ACE, angiotensin converting enzyme. Group A: pioglitazone first, then metformin; Group B: metformin first, then pioglitazone.

lated as weight (kg)/height$^2$ (m$^2$). Urinary albumin was measured with the latex agglutination assay provided by Special Reference Laboratories (SRL), Inc. (Tachikawa, Japan). For the OGTT, a 75-g glucose load was administered after a 12-h overnight fast. Blood was drawn immediately before ingestion and 30, 60, and 120 min after the glucose load. Homeotasis model assessment of insulin resistance (HOMA-IR) was calculated as follows (*13*).

$$\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mg/dl})]/405.$$

Blood samples were obtained between 8 AM and 10 AM on the same day that the OGTT was performed. Blood samples were collected into disposable, siliconized, evacuated glass tubes after 30 min bed rest in the supine position. The samples were centrifuged at 3,000 × *g* for 5 min at room temperature within 1 h of collection. The plasma was aliquoted in plastic tubes and stored at −80°C until use. Biochemical markers were measured in each facility. Insulin, inflammatory, hemostatic, and hormonal markers were measured in the SRL. Plasma adiponectin was measured with enzyme-linked immunosorbent assay (ELISA) using the human adiponectin ELISA kit (Otsuka Pharmaceuticals, Tokyo, Japan). Serum insulin and interleukin-6 (IL-6) were determined by the chemiluminescent enzyme immunoassay (CLEIA) system using the Eiken LS Reagent insulin kit for insulin and the human IL-6 CLEIA Fujirebio kit for IL-6. High-sensitivity C-reactive protein (hsCRP) was determined by nephelometry using the N-Latex CRP II N hsCRP kit. Plasma renin activity (PRA) was determined by the radio immunoassay double antibodies method using a renin activity (SRL) kit, and plasma aldosterone was determined by a radioimmunoassay solid-phase method using the SPAC-S aldosterone kit. Plasma noradrenaline was measured by high-performance liquid chromatography (HPLC) using CA test TOSOH reactive reagents D and E (TOSOH, Tokyo, Japan). Total PAI-1 (t-PA–PAI-1 complex) was determined by a latex photometric immunoassay (LPIA) using the LPIA·tPAI test kit. Von Willebrand factor (vWF) activity was determined by a platelet agglutination test using the von Willebrand Reagent kit, and *d*-dimer was determined by a latex turbidimetric immunoassay using the COBAS reagent *d*-dimer kit (Roche Diagnostics, Basel, Switzerland). Pulse wave velocity (PWV) and carotid augmentation index (AI) were examined by trained technicians with form ABI/PWV® (Omron Colin Co., Ltd., Tokyo, Japan). This device's accuracy and reproducibility were reported previously (*14*).

### Statistical Analysis

All statistical analyses were carried out with SPSS/Windows, version 13.0J (SPSS, Chicago, USA). The data were expressed as mean±SD or percentages. The Wilcoxon signed-rank test (two-tailed exact significance) was used to compare the differences between baseline, pioglitazone, and metformin. The modified Bonferroni correction (*15*) for multiple tests of significance was used to estimate significance. A two-sided $p$ value $<0.05$ was considered statistically significant.

## Results

The baseline characteristics of the 25 subjects who completed the study are shown in Table 1. Initially, 31 subjects were enrolled, but 6 subjects withdrew: 5 for personal reasons and 1 because of a finding of unexpectedly normal glucose when the first OGTT was done. Of the 5 patients who dropped out, 4 completed only the baseline examination and 1 completed only the pioglitazone therapy. Of the 25 subjects, 21 (84%) were hypertensive and 20 had taken antihypertensive drugs prior to their enrollment. Fourteen subjects were diagnosed as IGT and 11 as diabetes mellitus by WHO criteria. The mean dosage of pioglitazone was 15 mg and that of metformin was 740 mg.

As shown in Table 1, the baseline characteristics were not

**Table 2. Comparisons of Glycemic Factors before and after Treatments**

| | Baseline | Pioglitazone | Metformin |
|---|---|---|---|
| Glucose, fasting (mg/dl) | 113±12 | 107±10* | 110±13 |
| Glucose, 120 min (mg/dl) | 190±40 | 180±53 | 186±53 |
| Insuline, 0 min (μU/ml) | 9.9±5.7 | 6.7±3.1 | 7.7±5.3 |
| HOMA-IR | 2.8±1.7 | 1.7±0.8* | 2.1±1.5 |

*$p<0.05$ *vs*. baseline (modified Bonferroni correction for multiple tests of significance). Wilcoxon Signed Ranks Test (two-tailed exact significance) was used to compare the difference among the three variables. HOMA-IR, homeotasis model assessment of insulin resistance (μU/ml·mg/dl/405).

**Table 3. Comparisons of Metabolic Factors before and after Treatments**

| | Baseline | Pioglitazone | Metformin |
|---|---|---|---|
| Uric acid (mg/dl) | 5.7±1.3 | 5.4±1.1 | 5.9±1.4 |
| Cholesterol (mg/dl) | 201±31 | 198±29$^{\dagger}$ | 184±24* |
| HDL-C (mg/dl) | 57±14 | 58±14$^{\dagger}$ | 52±14* |
| Noradrenaline (pg/ml) | 431±357 | 328±173 | 351±294 |
| PRA (ng/ml/h) | 4.4±6.3 | 2.4±3.2 | 3.5±6.4 |
| Aldosterone (pg/ml) | 89±32 | 67±23* | 68±26* |
| Adiponectin (μg/ml) | 7.3±3.2 | 14.4±7.5*,$^{\dagger}$ | 7.6±3.4 |

*$p<0.01$ *vs*. baseline, $^{\dagger}p<0.01$ *vs*. metformin. Wilcoxon Signed Ranks Test (two-tailed exact significance) was used to compare the difference among the three variables. Modified Bonferroni correction for multiple tests of significance was used. HDL-C, high density lipoprotein cholesterol; PRA, plasma renin activity.

**Table 4. Comparisons of Hemostatic and Inflammatory Factors before and after Treatments**

| | Baseline | Pioglitazone | Metformin |
|---|---|---|---|
| Leukocyte (/μl) | 6,721±1,481 | 5,201±1,323*** | 5,378±1,159** |
| IL-6 (pg/ml) | 2.4±3.7 | 1.3±0.9 | 1.3±0.7 |
| hsCRP (ng/ml) | 3,034±6,504 | 670±599 | 842±859 |
| vWF activity (%) | 152±53 | 123±52* | 121±39* |
| *d*-Dimer (ng/ml) | 0.5±0.5 | 0.4±0.3 | 0.4±0.3 |
| Total PAI-1 (ng/ml) | 32±21 | 28±12 | 37±22 |

*$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs*. baseline (modified Bonferroni correction for multiple tests of significance). Wilcoxon Signed Ranks Test (two-tailed exact significance) was used to compare the difference among the three variables. IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; vWF, von Willebrand factor; Total PAI-1, t-PA–PAI-1 complex.

**Table 5. Comparisons of Hemodynamic Values before and after Treatments**

| | Baseline | Pioglitazone | Metformin |
|---|---|---|---|
| Systolic BP (mmHg) | 146±18 | 143±17 | 140±17 |
| Diastolic BP (mmHg) | 79±18 | 78±11 | 81±9 |
| Pulse rate (bpm) | 76±13 | 75±14 | 76±13 |
| Right PWV (cm/s) | 1,645±385 | 1,579±326 | 1,603±283 |
| Left PWV (cm/s) | 1,642±361 | 1,581±305 | 1,595±277 |
| Augmentation index (%) | 19±18 | 16±18 | 18±17 |

BP, blood pressure; PWV, pulse wave velocity. Wilcoxon Signed Ranks Test (two-tailed exact significance) was used to compare the difference among the three variables. Modified Bonferroni correction for multiple tests of significance was used to consider the significance.

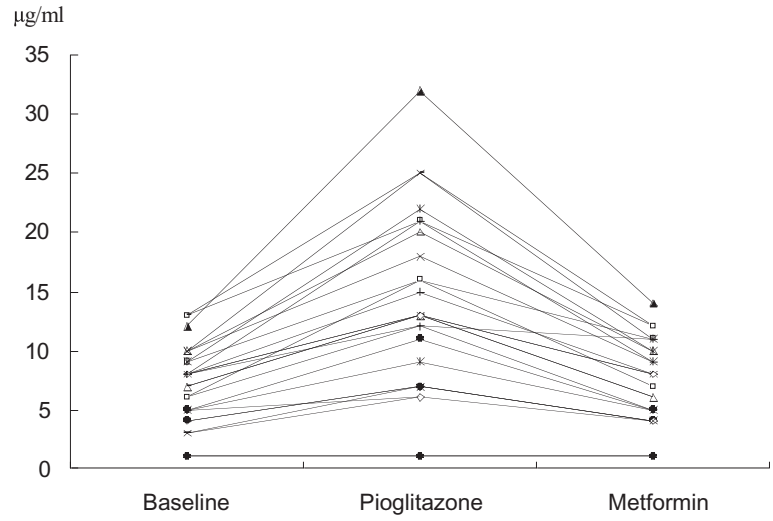


**Fig. 2.** *Change of adiponectin level at baseline and after pioglitazone or metformin therapy. The order of the administration of each drug was randomized so that either pioglitazone (*n = *13) or metformin was given first (*n = *12).*

significantly different between groups A and B. As a preliminary analysis, 23 variables used from Tables 2 to 5 were compared between groups A and B. When statistical significance was set as $p<0.1$, only leukocyte counts ($p=0.007$) differed between the two groups. To check the order effect of pioglitazone and metformin therapy, the variables after each drug therapy were compared between groups A and B within each treatment. Out of 23 variables, 3 (leukocyte $p=0.003$, adiponectin $p<0.001$, and PWV $p=0.085$) differed significantly between A and B in pioglitazone therapy, whereas 1 of 23 (leukocyte $p=0.059$) differed between A and B in metformin therapy. Therefore, leukocyte counts were excluded from this analysis. The variables not expected to change with these drug therapies, such as uric acid and catecholamins, showed no order effect. Therefore, the order effects can be ignored in this analysis.

Pioglitazone significantly reduced both FPG and HOMA-IR, but metformin did not change either (Table 2). Both treatments reduced 2-h glucose and fasting insulin levels, though not significantly. The hemoglobin A1c did not change with either treatment (baseline 5.7±0.3% *vs*. pioglitazone 5.7±0.4%, metformin 5.7±0.4%, n.s.).

Pioglitazone did not change cholesterol or high density lipoprotein (HDL) cholesterol (HDL-C), whereas metformin reduced both (Table 3). Triglycerides did not change significantly with either treatment (baseline 121±53 mg/dl *vs*. pioglitazone 109±49 mg/dl, metformin 125±58 mg/dl, both, n.s.) Plasma noradrenaline was slightly reduced with each drug, but not significantly (Table 3). Plasma aldosterone was significantly reduced with either drug, but PRA did not change significantly (Table 3). Plasma adiponectin was significantly increased by pioglitazone but not by metformin (Table 3, Fig. 2). The trend did not change even when the comparison was made only at baseline *vs*. 3 months; the increase in adiponectin (3 months minus baseline) with pioglitazone therapy tended to be higher than that with metformin (8.9±5.3 μg/ml *vs*. 5.4±3.8 μg/ml, $p=0.076$).

As shown in Table 4, hsCRP and IL-6 were reduced, but these changes were not significant. Although the vWF was significantly reduced with either drug, the *d*-dimer and the total PAI-1 did not change (Table 4). BP, heart rate, PWV, and carotid AI did not significantly change with either drug (Table 5).

During metformin therapy, 2 patients complained of diarrhea and 1 patient complained of appetite loss in the first 2 weeks after the drug was started. However, all of these symptoms were self-limiting. One patient presented mild facial edema during the pioglitazone therapy. However, no patients stopped their participation in this study due to adverse effects.

## Discussion

In this study, both pioglitazone and metformin reduced vWF and plasma aldosterone in subjects with IGT and early diabetes. In addition, pioglitazone, but not metformin, improved insulin sensitivity, and the increase in plasma adiponectin was greater than metformin. However, the hemodynamic factors, such as BP and PWV, did not change with either drug therapy.

Systemic inflammation is reported to be a strong predictor of atherosclerosis (*16*). Elevation of inflammatory markers is reported not only in diabetes but also in IGT. High BP itself is also an independent determinant of systemic inflammation (*17*). Pioglitazone reduced the inflammatory markers in both human diabetes mellitus (*18*, *19*) and a rat model of elastocalcinotic arteriosclerosis (*20*). Metformin is effective for reducing inflammatory markers in diabetes mellitus (*3*). In a study comparing troglitazone (another thiazolidinedione drug) and

metformin, CRP was reduced with both drugs (*21*). The mechanism underlying these anti-inflammatory effects has been attributed to the improvement of insulin resistance with these drugs. In the present study, both pioglitazone and metformin reduced IL-6 and hsCRP marginally. These two measures can be indicators of systemic inflammation (*22*). We can suggest two reasons why the changes in IL-6 and hsCRP did not reach statistical significance in this study. First, the dose of either drug was relatively low. The doses of pioglitazone (15 mg/day) and metformin (500–750 mg/day) were much lower than those usually reported: 45 mg/day (*18*) and 850 mg/day (*10*), respectively. Second, the study period might not have been long enough to produce a sufficient anti-inflammatory effect. In previous reports, the study periods were 6 months with pioglitazone (*18*) and 12 months with metformin (*3*).

Pioglitazone and metformin are anti-diabetic drugs, and both are specifically reported to effectively improve insulin resistance (*23*). Insulin resistance is also associated with the progression of atherosclerotic disease in a study of a Japanese population (*24*). Pioglitazone has anti-atherogenic effects (*19*) by increasing adiponectin, which is derived from adipose tissue (*25*). Adiponectin not only has an anti-atherosclerotic effect (*26*) but also can be a diagnostic marker of metabolic syndrome as reported in obese Japanese children (*27*); it is also a risk indicator in non-obese young men (*28*). In the present study, only pioglitazone significantly reduced fasting glucose and the HOMA-IR (*13*), and only pioglitazone increased adiponectin. These results indicate that only pioglitazone can improve insulin sensitivity through the improvement of adiponectin (*29*) in IGT or early diabetes subjects.

By a meta-analysis of diabetic patients, pioglitazone reduced plasma triglycerides and increased HDL-C, but had no beneficial effect on low density lipoprotein (LDL) cholesterol. On the other hand, metformin did not change lipid profiles in diabetics (*21*). In the present study, pioglitazone marginally reduced triglycerides but had no effect on cholesterol or HDL-C, whereas metformin reduced both cholesterol and HDL-C levels. The results for cholesterol were the same as those in a report on HIV lipodystrophy (*29*). In the present study, because the mean baseline cholesterol, triglycerides, and HDL-C were all within the normal range, the beneficial lipid-lowering effect of these drugs might not have appeared clearly.

There are few reports showing the effects of pioglitazone and metformin on the sympathetic nervous system or the renin-angiotensin aldosterone system. Although pioglitazone has been reported to have pleiotrophic effects, including a BP lowering effect (*30*), only an animal study showed a reduction in angiotensin II (*31*) with pioglitazone. In a report of healthy men, pioglitazone increased PRA and tended to increase aldosterone (*32*). In the present study, on the other hand, plasma aldosterone was significantly reduced and PRA tended to be reduced by both pioglitazone and metformin, but plasma noradrenaline did not change. Three mechanisms can be suggested to explain why PRA and aldosterone were decreased. First, the dose of pioglitazone was as low as 15 mg/day in the present study, whereas it was 45 mg/day in the report of Zanchi *et al*. (*32*). The mechanism underlying the increased PRA and aldosterone was attributable to vasodilation accompanied by reflex sympathetic hyperactivity (*32*). Peripheral edema due to thiazolidinediones can be caused by high dosages, fluid retention, circulating insulin, and reflex sympathetic hyperactivity (*33*, *34*). In the present study, none of the subjects presented peripheral edema except for one subject with mild facial edema. However, none of the subjects presented significant body weight gain or signs of sympathetic hyperactivity. Therefore, the main reason why PRA and aldosterone were decreased in the present study might be that sodium reabsorption by pioglitazone without vasodilation caused negative feedback of the renin-angiotensin-aldosterone system. Second, because 84% of the subjects took antihypertensive medication (mainly either diuretics, Ca channel blockers, or angiotensin II receptor blockers) that have diuretic and vasodilatory effects, the subjects' blood vessels tended to dilate. Third, the improvement of insulin sensitivity by both pioglitazone and metformin might indirectly have lowered aldosterone levels. This is supported by a report that insulin resistance is positively associated with PRA and plasma aldosterone level (*35*). vWF and PAI-1 are markers of endothelial function, and both are increased in IGT compared with normal glucose subjects (*36*, *37*). Metformin is reported to reduce PAI-1 antigen in insulin-resistant HIV patients (*38*) and in obese type 2 diabetics (*39*) through the improvement of hyperinsulinemia and insulin resistance. However, pioglitazone did not change either vWF (*8*, *18*) or total PAI-1 (*18*, *21*) in previous reports of type 2 diabetes. In the present study, although pioglitazone and metformin significantly lowered vWF, neither total PAI-1 nor the *d*-dimer changed. The improvement of insulin resistance observed only in pioglitazone therapy might not be relevant to the result. Further studies are needed to clarify this issue.

Pioglitazone is reported to improve arterial stiffness in animals (*20*) and human diabetic subjects (*40*); to have beneficial antiproliferative, antifibrotic (*41*), and anti-elastocalcinosis effects; and to increase NOx excretion (*42*). The association of PWV with insulin resistance was reported in a general population (*43*) and in non-diabetic hypertensive subjects (*44*). In the present study, PWV and aortic AI were marginally reduced with pioglitazone therapy, but that was not statistically significant. Three possible reasons can be considered: the short duration of the study, the small sample size, and the low PWV and AI at baseline. Further studies on this issue are needed.

In conclusion, in subjects with IGT and early diabetes, although pioglitazone had different benefits from metformin on insulin resistance and adiponectin, both drugs equally reduced vWF and aldosterone even at low doses and after short medication periods. Early intervention with these drugs can be an option for IGT or early phase diabetes.

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