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Effects of Replacing Metformin with Pioglitazone on Glycemic Control in Japanese Patients with Poorly Controlled Type 2 Diabetes Mellitus: A 12-Week, Open-Label, Prospective Study

Shinji Sakaue, MD[1]; Mitsunori Kamigaki, MD[1]; Haruhiko Yoshimura, MD[2]; and Masaharu Nishimura, MD[1]

[1]*First Department of Medicine, Hokkaido University School of Medicine, Sapporo, Japan; and* [2]*Department of Internal Medicine, Iwamizawa Municipal General Hospital, Iwamizawa, Japan*

ABSTRACT

BACKGROUND: Insulin resistance is a critical aspect of the pathophysiology of type 2 diabetes mellitus and is also associated with other risk factors for cardiovascular disease (eg, dyslipidemia and hypertension). Accordingly, insulin resistance is a possible target for lowering plasma glucose concentration and preventing diabetic macroangiopathy. Biguanides, such as metformin, and thiazolidinediones (TZDs), such as pioglitazone, improve insulin resistance.

OBJECTIVES: The aims of this study were to assess the effects of replacing a biguanide with a TZD on glycemic control in patients with poorly controlled type 2 diabetes mellitus, and also to identify the factors affecting interpatient variation in the effects of treatment change.

METHODS: This was a 12-week, open-label, prospective study in which previously prescribed metformin (500 or 750 mg/d) was replaced with pioglitazone (15 or 30 mg/d) in patients with poorly controlled type 2 diabetes mellitus. Patients with a glycosylated hemoglobin (HbA_{1c}) concentration >7% despite treatment with diet, exercise, and hypoglycemic agents other than TZDs were eligible for the study. Patients who never received TZDs were also eligible for inclusion. Vital signs, metabolic parameters, and arterial stiffness were assessed at baseline and after 12 weeks of treatment with pioglitazone. The primary end point was change in HbA_{1c} concentration after replacing metformin with pioglitazone. Tolerability was assessed by medical history, physical examination, and laboratory tests (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase).

RESULTS: Twenty-one Japanese patients (15 women, 6 men; mean [SD] age, 61.8 [8.4] years; body mass index, 25.5 [3.0] kg/m^2) were included in the study. HbA_{1c} concentration was not significantly changed from baseline after 12 weeks of pioglitazone treatment (8.0% [0.7%] vs 8.2% [0.7%]). Fasting plasma glucose (FPG) concentration also was not significantly changed after the replacement of treatment

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(156 [27] vs 144 [30] mg/dL). In addition, the resistin concentration did not change significantly from baseline after 12 weeks of pioglitazone treatment (6.6 [3.8] vs 6.4 [3.6] ng/mL). In contrast, significant improvement from baseline was observed in triglyceride (TG) concentrations (157 [109] vs 117 [68] mg/dL; $P = 0.003$), high-density lipoprotein cholesterol (HDL-C) (55 [12] vs 61 [16] mg/dL; $P = 0.016$), remnant-like particle cholesterol (6.6 [6.0] vs 5.3 [3.5] mg/dL; $P = 0.048$), and serum adiponectin (8.8 [4.3] vs 23.3 [11.7] μg/mL; $P < 0.001$). Pulse wave velocity was also significantly improved (1730 [361] vs 1622 [339] m/sec; $P = 0.009$). Changes in HbA_{1c} were significantly correlated with serum fasting insulin concentration at baseline in the patients not receiving insulin preparations ($r = -0.635$, $P = 0.013$). The percentage change in serum adiponectin concentration was correlated with the percentage changes in HbA_{1c} and FPG concentrations (HbA_{1c}, $r = -0.518$, $P = 0.019$; FPG, $r = -0.594$, $P = 0.006$). Body weight was significantly increased after treatment (62.6 [11.9] vs 65.5 [12.2] kg; $P < 0.001$). Mild edema was reported in 5 patients. One patient discontinued treatment due to an increase in serum creatine kinase activity to ~6.6 times the upper limit of normal.

CONCLUSIONS: Replacement of metformin with pioglitazone did not produce significant differences in HbA_{1c} and FPG concentrations from baseline after 12 weeks of treatment in these patients with poorly controlled type 2 diabetes mellitus. However, the replacement was effective in a subset of patients whose serum insulin concentrations were high or whose serum adiponectin concentrations were sensitive to TZDs. In addition, the replacement was associated with significant improvements in TG, HDL-C, serum adiponectin concentration, pulse wave velocity, and body weight increase from baseline. (*Curr Ther Res Clin Exp.* 2008;69:364–377) © 2008 Excerpta Medica Inc.

KEY WORDS: insulin resistance, metformin, pioglitazone, Japanese.

INTRODUCTION

Insulin resistance is a critical aspect in the pathophysiology of type 2 diabetes mellitus[1] and is also associated with other risk factors for cardiovascular disease (eg, dyslipidemia and hypertension).[2] Accordingly, insulin resistance is a possible target for lowering plasma glucose concentration and preventing diabetic macroangiopathy.

Biguanides, such as metformin, and thiazolidinediones (TZDs), such as pioglitazone, improve insulin resistance.[3] Both drugs are useful for metabolic control in patients with type 2 diabetes mellitus. Although the mechanism of action of metformin remains unclear, it is primarily found to reduce hepatic glucose output.[4] Adenosine monophosphate–activated protein kinase has been proposed as the molecular mechanism of action in metformin.[5] In contrast to metformin, TZDs seem to promote glucose disposal rather than being responsible for the inhibition of endogenous glucose production.[4] The TZD troglitazone is a ligand of peroxisome proliferator-activated receptor γ that induces adipocyte differentiation, making adipocytes small and insulin-sensitive.[6] Therefore, there are differences in the mechanisms of action of the 2 drugs.

The effects of metformin and pioglitazone have been compared in randomized trials.[7,8] The overall reductions of glycosylated hemoglobin (HbA_{1c}) concentrations were found to be similar in the 2 treatment groups (metformin vs pioglitazone: –1.5% vs –1.3%[7] and –1.5% vs –1.4%[8]). However, it remains to be determined whether the 2 drugs have similar glucose-lowering effects in subsets of patients with type 2 diabetes mellitus because the effect of TZDs is known to vary among individuals.[9,10] In the postmarketing surveillance study of Japanese type 2 diabetes mellitus patients treated with pioglitazone, the relationship between change in HbA_{1c} and body mass index (BMI) or insulin level was not statistically analyzed.[11]

The aims of this study were to compare glucose control, metabolic parameters, and risk factors of atherosclerosis before and after replacing metformin with pioglitazone in patients with poorly controlled type 2 diabetes mellitus and also to identify the factors affecting interpatient variation in the effects of treatment change.

PATIENTS AND METHODS

PATIENTS

We recruited patients with type 2 diabetes mellitus from Hokkaido University Hospital (Sapporo, Japan) and Iwamizawa Municipal General Hospital (Iwamizawa, Japan) who were receiving metformin (500 or 750 mg/d) and who were not optimally controlled. These are the dosages that are approved and typically prescribed in Japan as described elsewhere.[12,13]

Patients with an HbA_{1c} concentration >7% despite treatment with diet, exercise, and hypoglycemic agents other than TZDs and who had never received TZDs were eligible for the study. Patients with any of the following conditions were excluded: heart failure; diabetic nephropathy with proteinuria or increased serum creatinine concentration (>1.0 mg/dL); uncontrolled diabetic retinopathy; liver dysfunction (aspartate aminotransferase activity >100 U/L or alanine aminotransferase [ALT] activity >100 U/L); or pregnancy.

Patients who met the inclusion criteria and agreed to participate were consecutively recruited in the study. This study was approved by the Institutional Review Board of Hokkaido University Hospital (Sapporo, Japan) and was carried out according to the Declaration of Helsinki.[14] Written informed consent was obtained from all participants. There was no compensation for study participation.

STUDY DESIGN

This was a 12-week, open-label, prospective study in which previously prescribed metformin (500 or 750 mg/d) was replaced with pioglitazone (15 or 30 mg/d) in patients with poorly controlled type 2 diabetes mellitus. The patients were instructed to replace metformin with pioglitazone (15 mg once daily, after breakfast) on the day following study entry. Four weeks after drug replacement, the patients were assessed for adverse events (AEs) using medical history, physical examination, and liver function tests. If no AEs were observed, the pioglitazone dose was increased to 30 mg once daily. Tolerability was checked at weeks 8 and 12. Medication compliance was monitored by patient report at weeks 8 and 12 as well. Visits that were delayed ≤2 weeks

were permitted. Administration of pioglitazone was continued until week 12. Other medications were unchanged during the study.

MEASUREMENTS

BMI was calculated using the following equation: body weight (kg)/height (m^2). Blood pressure (BP) was measured using a sphygmomanometer with subjects in the sitting position by physicians who were not blinded to the study objectives or methods. Mean BP was calculated using the following equation:

$$\text{diastolic BP} + (\text{systolic BP} - \text{diastolic BP})/3.$$

Metabolic parameters were examined at baseline and week 12 to evaluate the effects of the drug substitution. Blood sampling was performed in the morning after overnight fasting. For measurements of fasting plasma glucose (FPG) and HbA_{1c} concentrations, blood was collected in plastic tubes including NaF and Na_2-ethylenediamine tetraacetic acid and centrifuged, and the resultant plasma was used. Concentrations of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), remnant-like particle cholesterol (RLP-C), and lipoprotein a (Lp(a)) were measured for comparison with lipid profiles and serum adiponectin, and resistin concentrations were measured for comparison with serum adipocytokine concentration. Serum used for those measurements were prepared by centrifugation of blood collected in plastic tubes including no anticoagulant.

To assess arterial stiffness, brachial-ankle pulse wave velocity (PWV) was measured at baseline and week 12 using volume plethysmography (Form PWV/ABI, Colin Co. Ltd., Komaki, Japan). The measurements were done by laboratory technicians who were blinded to the aims of the study. A mean of right and left measurements was used for the analysis.

OUTCOME MEASUREMENTS

The primary variable was change in HbA_{1c} concentration. Secondary parameters included FPG concentration, fasting plasma lipid concentrations, adipocytokines, BP, PWV, and body weight.

The relationships between changes in HbA_{1c} concentration and secondary parameters (FPG concentration, fasting plasma lipid concentrations, adipocytokines, BP, PWV, and body weight) were also tested.

STATISTICAL ANALYSIS

The data analyses were performed as intent-to-treat. Measured parameters at 0 and 12 weeks were compared using the paired *t* test. Sample size was based on the primary end point (change in HbA_{1c} concentration after 12 weeks of treatment with pioglitazone). Based on the findings of a previous study,[8] when the SD of differences in HbA_{1c} changes was assumed to be 1.0, for a 2-sided paired *t* test to detect a 0.7% difference in HbA_{1c} concentration with 5% significance and 80% power, a sample size of ≥19 patients was needed. The changes in HbA_{1c} concentration and secondary parame-

ters measured at baseline were analyzed to obtain Pearson's correlation coefficients. The relationship between the percentage changes in HbA_{1c} or FPG concentrations and those of the secondary measured parameters were similarly analyzed. Values were presented as mean (SD). Differences were considered significant at $P < 0.05$.

RESULTS

PATIENTS

Twenty-one Japanese patients (15 women, 6 men; mean [SD] age, 61.8 [8.4] years) were included in the study. Twenty patients were receiving metformin 750 mg/d, and 1 patient was receiving metformin 500 mg/d. Baseline characteristics, including the drugs used at baseline, are shown in **Table I**. Mean BMI was 25.5 (3.0) kg/m^2, which is above the cutoff value for a diagnosis of obesity in Japan.[15] At baseline, 11 patients were receiving treatment for hypertension, and 12 were receiving treatment for dyslipidemia.

Vital signs and laboratory findings at baseline and after 12 weeks of pioglitazone treatment are shown in **Table II**. The baseline blood glucose concentration was unsatisfactory, which could be accounted for by the inclusion criteria (HbA_{1c}, 8.0% [0.7%]; FPG, 156 [27] mg/dL). At baseline, systolic BP was 135 (19) mm Hg, diastolic BP was 78 (12) mm Hg, and mean BP was 97 (12) mm Hg. TG and RLP-C concentrations were elevated (TG, 157 [109] mg/dL; RLP-C, 6.6 [6.0] mg/dL). These findings suggested impaired lipoprotein metabolism.

Serum insulin concentration was determined in the 14 patients among those who did not receive insulin therapy (7.6 [6.3] μU/mL). Two patients had RLP-C concentration values below the measurable limit (2.0 mg/dL) after 12 weeks of treatment and 1 patient had a Lp(a) concentration value below the measurable limit (1.0 mg/dL) throughout the study. These values were not included in the analysis. If the minimum values within the measurable ranges were applied to the analysis instead of those subminimal values, the results did not differ.

One patient did not complete the 12-week study because of an increase in serum creatine kinase activity. Of the 20 patients who did complete the study, 1 patient did not have a laboratory test at week 8 but continued to receive pioglitazone for the 12-week treatment period. In 1 patient, an increase in the dose of pioglitazone was postponed until week 8 due to edema.

EFFECTS OF DRUG REPLACEMENT

Glycemic control, evaluated using HbA_{1c} concentration, did not significantly change from baseline after 12 weeks of treatment (8.0% [0.7%] vs 8.2% [0.7%]) (**Figure 1A**). FPG concentration was also unchanged (156 [27] vs 144 [30] mg/dL) (**Figure 1B**). However, individual differences were found: HbA_{1c} and FPG concentrations decreased in 6 and 11 patients, respectively.

With regard to lipid metabolism, TC concentration did not significantly change from baseline after 12 weeks of treatment (194 [35] vs 192 [39] mg/dL). TG concentration decreased significantly (157 [109] vs 117 [68] mg/dL; $P = 0.003$) and HDL-C concentration increased significantly (55 [12] vs 61 [16] mg/dL; $P = 0.016$). RLP-C

Table I. Baseline demographic and clinical characteristics of the Japanese study patients (N = 21).

Characteristic	Value
Age, mean (SD), y	61.8 (8.4)
Sex, no. (%)	
Female	15 (71.4)
Male	6 (28.6)
Duration of diabetes, mean (SD), y	10.3 (5.1)
Body mass index, mean (SD), kg/m^2	25.5 (3.0)
Drugs taken at baseline, no.	
Antidiabetic drugs, except biguanides	
Sulfonylureas only	7
Sulfonylureas + α-GI	6
Insulin only	2
Nateglinide + α-GI	2
Nateglinide only	1
Insulin + α-GI + nateglinide	1
None	2
Antihypertensive drugs*	
ARBs	10
Calcium channel blockers	5
Diuretics	3
ACE inhibitors	3
α-Blockers	2
β-Blockers	2
Lipid-lowering drugs	
Statins	12
Niacin	0

α-GI = α-glucosidase inhibitor; ARBs = angiotensin II receptor blockers; ACE = angiotensin-converting enzyme.
*Some patients were receiving >1.

concentration also decreased significantly (6.6 [6.0] vs 5.3 [3.5] mg/dL; $P = 0.048$). However, Lp(a) concentration did not change significantly (15.7 [21.5] vs 18.3 [21.4] mg/dL). Serum adiponectin concentration increased in all patients (8.8 [4.3] vs 23.3 [11.7] μg/mL; $P < 0.001$), whereas the resistin concentration did not change significantly from baseline after 12 weeks of pioglitazone treatment (6.6 [3.8] vs 6.4 [3.6] ng/mL). PWV decreased significantly (1730 [361] vs 1622 [339] m/sec; $P = 0.009$) (Table II).

Table II. Vital signs and laboratory findings at baseline and after replacing metformin with pioglitazone for 12 weeks in Japanese patients with poorly controlled type 2 diabetes mellitus. Data are mean (SD).

Variable	Baseline	Week 12	*P*
Mean blood pressure, mm Hg	97 (12)	93 (13)	0.150
Body weight, kg	62.6 (11.9)	65.5 (12.2)	<0.001
Fasting plasma glucose, mg/dL	156 (27)	144 (30)	0.139
Glycosylated hemoglobin, %	8.0 (0.7)	8.2 (0.7)	0.450
Total cholesterol, mg/dL	194 (35)	192 (39)	0.955
Triglycerides, mg/dL	157 (109)	117 (68)	0.003
HDL-C, mg/dL	55 (12)	61 (16)	0.016
RLP-C, mg/dL	6.6 (6.0)	5.3 (3.5)	0.048
Lipoprotein(a), mg/dL	15.7 (21.5)	18.3 (21.4)	0.100
Insulin, μU/mL	7.6 (6.3)	6.6 (3.9)	0.119
Adiponectin, μg/mL	8.8 (4.3)	23.3 (11.7)	<0.001
Resistin, ng/mL	6.6 (3.8)	6.4 (3.6)	0.590
Pulse wave velocity, m/sec	1730 (361)	1622 (339)	0.009
Aspartate aminotransferase, U/L	25 (10)	23 (8)	0.172
Alanine aminotransferase, U/L	29 (14)	22 (9)	0.001

HDL-C = high-density lipoprotein cholesterol; RLP-C = remnant-like particle cholesterol.

RELATIONSHIP BETWEEN GLYCEMIC CONTROL AND ADIPONECTIN CONCENTRATION

The change in HbA_{1c} concentration was significantly correlated with serum fasting insulin concentration at baseline in patients not receiving insulin ($r = -0.635$, $P = 0.013$) (**Table III**). In addition, the percentages of the changes in HbA_{1c} and FPG concentrations were correlated with the percentage of the change in adiponectin (HbA_{1c}, $r = -0.518$, $P = 0.019$; FPG, $r = -0.594$, $P = 0.006$) (**Figure 2**).

TOLERABILITY AND SAFETY PROFILE

Body weight increased significantly (62.6 [11.9] vs 65.5 [12.2] kg; $P < 0.001$) after 12 weeks of pioglitazone treatment (**Table II**). Mild edema was reported in 5 patients, while no patient experienced hepatotoxicity. ALT activity decreased (29 [14] vs 22 [9] U/L; $P = 0.001$). At week 8, 1 patient discontinued the study due to an increase in serum creatine kinase activity, which was ~6.6 times the upper limit of normal, although there were no associated symptoms. After discontinuing pioglitazone treatment, the serum creatine kinase activity normalized (213 U/L at baseline vs 1192 U/L at week 8 vs 94 U/L at week 12).

DISCUSSION

In this study, we assessed the effects of replacing metformin with pioglitazone in patients with poorly controlled type 2 diabetes mellitus. HbA_{1c} concentration was

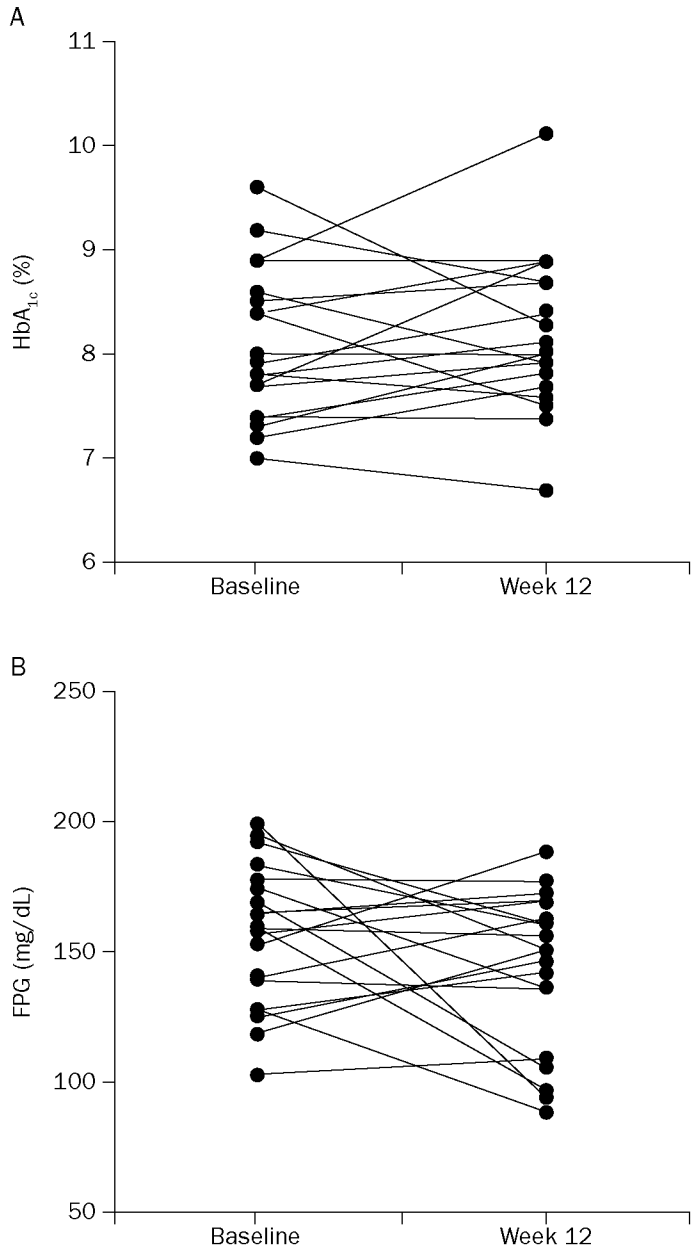

Figure 1. Changes in (A) glycosylated hemoglobin (HbA_{1c}) and (B) fasting plasma glucose (FPG) concentrations 12 weeks after replacing metformin with pioglitazone in Japanese patients with poorly controlled type 2 diabetes mellitus.

Table III. Correlation analysis of the association between a change in glycosylated hemoglobin concentration and baseline vital signs and laboratory findings.

Variable	Correlation Coefficient	*P*
Mean blood pressure, mm Hg	0.224	0.349
Body weight, kg	−0.214	0.371
Fasting plasma glucose, g/dL	−0.382	0.097
Glycosylated hemoglobin, %	−0.428	0.059
Total cholesterol, mg/dL	0.214	0.370
Triglycerides, mg/dL	0.293	0.213
HDL-C, mg/dL	−0.075	0.758
RLP-C, mg/dL	0.285	0.227
Lipoprotein(a), mg/dL	0.071	0.777
Insulin, μU/mL	−0.635	0.013
Adiponectin, μg/mL	0.131	0.588
Resistin, ng/mL	−0.087	0.718
Pulse wave velocity, m/sec	0.119	0.623
Aspartate aminotransferase, U/L	−0.221	0.354
Alanine aminotransferase, U/L	−0.157	0.515

HDL-C = high-density lipoprotein cholesterol; RLP-C = remnant-like particle cholesterol.

unchanged 12 weeks after replacement, corresponding with the findings of other randomized, placebo-controlled studies.[7,8] However, there was a subset group in which HbA_{1c} had opposite outcome measures—it improved in one group of patients and it deteriorated in another group of patients. These findings suggest that replacing metformin with pioglitazone is useful for glycemic control in some patients.

The reduction in HbA_{1c} concentration was significantly correlated with serum fasting insulin concentration at baseline. This is compatible with the results of an observational study in which the glucose-lowering effect of pioglitazone was found to be greater in patients with high insulin concentrations.[11] In patients whose insulin concentrations are high, the transition from metformin to pioglitazone therapy may be effective.

After drug replacement, serum adiponectin concentration significantly increased in 12 weeks. TZDs, including pioglitazone, have been reported to increase serum adiponectin concentration,[16–18] whereas no increase in adiponectin concentration was found with metformin therapy.[19] The results in this study supported the effect of pioglitazone on serum adiponectin concentration. This increase may be favorable for the prevention of cardiovascular disease and enhancement of insulin sensitivity.[20] We found a correlation between the change in plasma glucose concentration and the change in serum adiponectin concentration, which suggests that the glucose-lowering effect of pioglitazone is likely to be linked to an increased adiponectin concentration. This finding supports a previous study[21] that reported the correlation between an

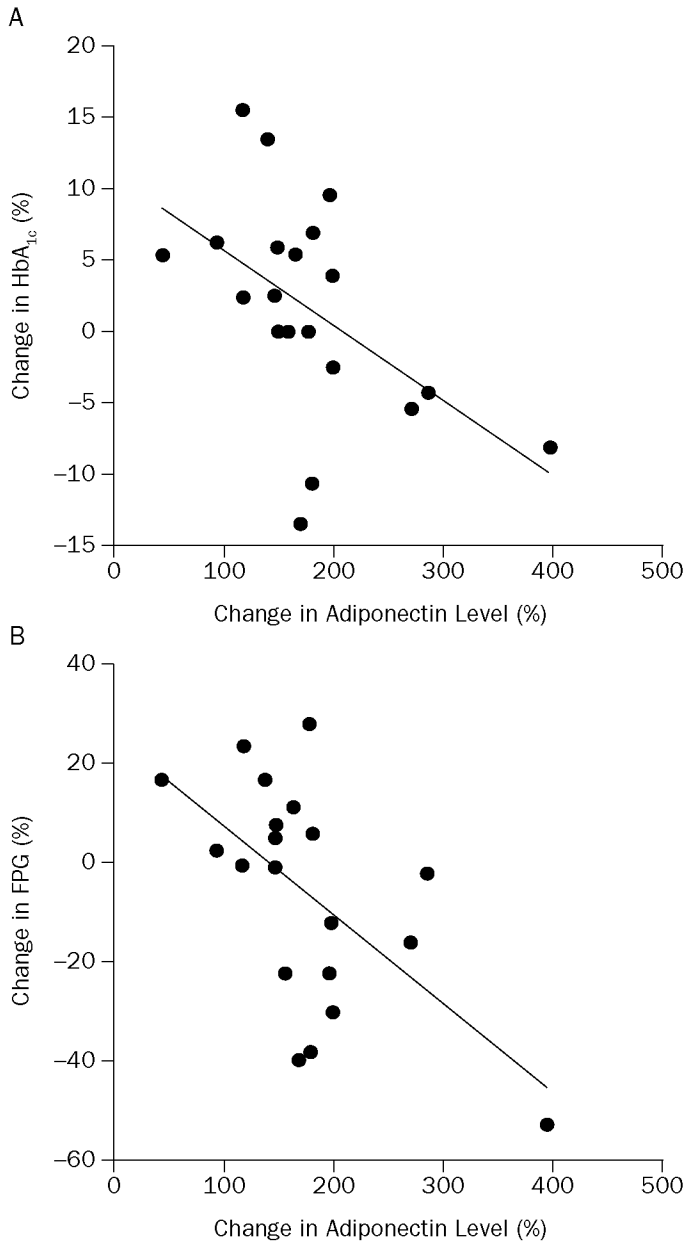

Figure 2. Correlation of percentage changes in (A) glycosylated hemoglobin (HbA_{1c}) (r = −0.518, P = 0.019) and (B) fasting plasma glucose (FPG) concentrations with those of serum adiponectin concentrations (r = −0.594, P = 0.006) 12 weeks after replacing metformin with pioglitazone in Japanese patients with poorly controlled type 2 diabetes mellitus.

increase in plasma adiponectin concentration and improvement in insulin sensitivity by pioglitazone evaluated with a euglycemic insulin clamp in subjects with uncontrolled type 2 diabetes mellitus who were receiving a stable dose of sulfonylurea. Although it has been proposed that TZD ameliorates glucose tolerance via not only adiponectin-dependent but also adiponectin-independent pathways in experiments using animal models,[22] adiponectin secretion capacity seems to be a key factor in association with the glucose-lowering effect of pioglitazone.

Replacing metformin with pioglitazone was associated with significant changes in the lipid profile. Concentrations of TG and HDL-C both improved significantly after drug replacement, supporting the findings of a previous randomized, double-blind study comparing pioglitazone with metformin in drug-naive patients with type 2 diabetes mellitus.[8] A significant decrease in RLP-C concentration was also observed in the present study. Therefore, in cases with such lipid abnormalities, which are often seen in obese patients, pioglitazone may be an option for patients poorly controlled on metformin.

We found that PWV was significantly decreased after the transition to pioglitazone treatment. This finding is in agreement with that of Satoh et al,[23] a prospective, nonplacebo-controlled study in Japanese patients with type 2 diabetes mellitus, who reported that pioglitazone improved PWV independent of its antidiabetic effect. Because PWV is not only an index of vascular stiffness but also predicts mortality and cardiovascular diseases,[24–26] our findings suggested that pioglitazone had favorable effects on vascular risk for at least 12 weeks.

The present study found that pioglitazone increased body weight, as shown previously,[27,28] although glycemic control was unchanged. Promotion of pioglitazone should be avoided in treating type 2 diabetes mellitus in obese patients. It is well known that metformin causes less weight gain and is advantageous in treating obese patients with diabetes.[29,30]

There were no cases of liver toxicity in this study, although 1 patient discontinued the study at week 8 due to an increase in serum creatine kinase activity. Serum ALT activity decreased rather than increased after drug replacement. This may be because steatosis was more improved by pioglitazone[31,32] than metformin, although metformin was also found to have a favorable effect on fatty liver disease.[33–35]

LIMITATIONS

This study had several limitations. A crossover study would have been more appropriate to examine the effect of drug replacement in each individual. In addition, the number of patients was small and no control group was used. Another limitation was using patients' reports to establish adherence to treatment and to assess AEs, which created recall bias. Although correlations between a change in HbA_{1c} concentration and various parameters were tested for exploratory analysis, there was no adjustment for multiple comparisons.

Patients enrolled in this study had been receiving 500 or 750 mg/d of metformin. The dosage of 750 mg/d is the maximum recommended for the treatment of diabetes in Japan. This dosage is smaller than that used in other countries.[12,13] Use of a higher

dose of metformin, which is more effective in glycemic control than a lower dose,[36] may have achieved control in these patients.

CONCLUSIONS

Replacement of metformin with pioglitazone did not produce significant differences in HbA_{1c} and FPG concentrations from baseline after 12 weeks of treatment in these patients with poorly controlled type 2 diabetes mellitus. However, the replacement was effective in a subset of patients whose serum insulin concentrations were high or whose serum adiponectin concentrations were sensitive to TZDs. In addition, the replacement was associated with significant improvements in TG, HDL-C, serum adiponectin concentration, PWV, and body weight increase from baseline.

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This study was designed by Drs. Sakaue, Yoshimura, and Nishimura. Study implementation was conducted by Drs. Sakaue, Kamigaki, and Yoshimura. Dr. Kamigaki performed all study analyses. The manuscript was written by Drs. Sakaue and Nishimura.

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ADDRESS CORRESPONDENCE TO: Shinji Sakaue, MD, First Department of Medicine, Hokkaido University School of Medicine, Sapporo 060-8638, Japan. E-mail: sakaue-s@med.hokudai.ac.jp