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Effect of Pioglitazone Compared with Metformin on Glycemic Control and Indicators of Insulin Sensitivity in Recently Diagnosed Patients with Type 2 Diabetes

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Pioglitazone, a thiazolidinedione, improves glycemic control primarily by increasing peripheral insulin sensitivity in patients with type 2 diabetes, whereas metformin, a biguanide, exerts its effect primarily by decreasing hepatic glucose output. In the first head-to-head, double-blind clinical trial comparing these two oral antihyperglycemic medications (OAMs), we studied the effect of 32-wk monotherapy on glycemic control and insulin sensitivity in 205 patients with recently diagnosed type 2 diabetes who were naive to OAM therapy. Subjects were randomized to either 30 mg pioglitazone or 850 mg metformin daily with titrations upward to 45 mg (77% of pioglitazone patients) and 2550 mg (73% of metformin patients), as indicated, to achieve fasting plasma glucose levels of less than 7.0 mmol/liter (126 mg/dl). Pioglitazone was comparable to metformin in improving glycemic control as measured by hemoglobin A1C and fasting plasma glucose. At endpoint, pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin ($P = 0.003$) and by analysis of homeostasis model assessment for insulin sensitivity (HOMA-S; $P = 0.002$). Both OAM therapies were well tolerated. Therefore, pioglitazone and metformin are equally efficacious in regard to glycemic control, but they exert significantly different effects on insulin sensitivity due to differing mechanisms of action. The more pronounced improvement in indicators of insulin sensitivity by pioglitazone, as compared with metformin monotherapy in patients recently diagnosed with type 2 diabetes who are OAM-naive, may be of interest for further clinical evaluation. (*J Clin Endocrinol Metab* 88: 1637–1645, 2003)

INSULIN RESISTANCE AND relative insulin deficiency contribute to the pathogenesis of type 2 diabetes. Insulin resistance, which plays the major role early in the evolution of the disease, is associated with clusters of cardiovascular risk factors (*e.g.* hypertension and dyslipidemia) that contribute to increased risk for coronary heart disease (1, 2). Presently, objectives for treatment of type 2 diabetes include not only normalization of hyperglycemia, but also reduction of hypertension and correction of dyslipidemia (3, 4). Directly targeting underlying insulin resistance in the periphery is a relatively new approach for treating type 2 diabetes. Beyond enhancements in glycemic control, reduction of insulin resistance may confer beneficial changes in additional components of insulin resistance syndrome, independent of improvements in glucose metabolism (5). Thus, oral antihyperglycemic medication (OAM) therapies that target elevated insulin resistance are rational treatment strategies that also improve the cardiovascular risk profile.

Pioglitazone is a thiazolidinedione (TZD) insulin sensitizer (5). As a nuclear peroxisome proliferator-activated receptor γ (PPAR-γ) agonist, it improves blood glucose and plasma lipoprotein profiles by modulating the transcription of genes that play key roles in carbohydrate and lipid metabolism, respectively (6). Pioglitazone may also improve endothelial dysfunction and other inflammatory conditions in the vasculature (5). Similar to other TZDs, including troglitazone (7, 8) and rosiglitazone (9), pioglitazone has been shown to enhance insulin sensitivity in the peripheral organs and the liver, resulting in improved glycemic control in patients with type 2 diabetes (10–13). In these patients, pioglitazone also lowers elevated plasma free fatty acids and improves diabetic dyslipidemia [low HDL-cholesterol (HDL-C) and high triglycerides (TGs); Ref. 13].

Metformin (a biguanide) improves glycemic control primarily by sensitizing the liver to the effects of insulin, thus decreasing hepatic insulin resistance and glucose output through a reduction in gluconeogenesis. Metformin also increases glucose use as a consequence of its insulin-sensitizing effect in the periphery (14–17). In addition, metformin has been found to improve the lipoprotein profile and induce weight reduction. The benefits of metformin have been as-

Abbreviations: A1C, Hemoglobin A1C; ALT, alanine transaminase; ANCOVA, analysis of covariance; ApoB, apolipoprotein B; AST aspartate transaminase; BP, blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-S, HOMA for insulin sensitivity; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); OAM, oral antihyperglycemic medications; TEAE, treatment-emergent adverse event; TG, triglyceride; TZD, thiazolidinedione.

sociated with a reduction in both microvascular and macrovascular complications in an overweight subset of patients in the United Kingdom Prospective Diabetes Study (UKPDS; Ref. 18).

Both pioglitazone and metformin are first-line therapeutic interventions in the management of type 2 diabetes patients, but their mechanisms of action are different and there are no data that directly compare their antihyperglycemic efficacy, their effects on insulin resistance, or their tolerability in recently diagnosed OAM-naive patients. Therefore, we compared the efficacy and tolerability of monotherapy with pioglitazone to metformin in this population. The primary objective of the study was to compare the effect of each treatment on glycemic control, as defined by change in hemoglobin A1C (A1C).

Subjects and Methods

Study design

A double-blind, multicenter, randomized, 32-wk comparator-controlled clinical trial was conducted in Russia and Hungary involving patients with recently diagnosed (<12 months) type 2 diabetes mellitus as defined by World Health Organization (WHO) Classification for Diabetes (19). The study design is depicted in Fig. 1.

At visit 1, laboratory tests were performed to determine patient eligibility; patients also received diabetes education and individualized dietary and physical activity instructions. During the lead-in period, patients took one placebo capsule and three placebo tablets daily for 3–5 wk, with continued administration of one capsule and three tablets daily throughout the course of the study to maintain the double-blind study design. At the baseline visit (visit 2), randomization was stratified on the basis of moderately high (7.5–9.0%) or high (>9.0–11%) A1C, with equal distribution across the two treatment groups. Patients randomized to pioglitazone took one 30-mg pioglitazone capsule and three placebo tablets daily for the 8-wk titration period (between visits 2 and 3). Patients randomized to metformin took one placebo capsule, one 850-mg metformin tablet, and two placebo tablets identical to the metformin tablet. Two weeks after randomization, patients in the metformin treatment group automatically increased dosage to two 850-mg metformin tablets/day (1700 mg metformin), one placebo capsule, and one placebo tablet daily for 6 additional weeks. At visit 3, for patients with fasting plasma glucose (FPG) at least 7.0 mmol/liter (126 mg/dl), the dose of pioglitazone was increased to one 45-mg capsule daily with continuation of three placebo tablets daily, or the dose of metformin was increased to three 850-mg tablets (2550 mg metformin) and one placebo capsule daily. During the remaining 24-wk treatment period, the study medication was administered as the equivalent of the final dose determined at visit 3.

At each visit, patient compliance was assessed and recorded on the basis of an individual determination of each patient's metabolic control, adherence to the visit schedule, adherence to diet and exercise plan, diabetes education, and the amount of returned medication, along with other parameters as deemed appropriate by the investigator.

Subjects

All patients enrolled in the study had an A1C level of 7.5–11.0% and were at least 40 yr old. Patients were not admitted to the study if any of the following criteria were present: history of lactic acidosis, liver disease, New York Heart Association Cardiac Status Class III or IV congestive heart failure, HIV infection, or a renal transplant; impaired kidney function; impaired liver function [aspartate transaminase (AST) or alanine transaminase (ALT) $\geq 2.5 \times$ the upper limit of the normal range]; body mass index below 25 or above 40 kg/m^2; breastfeeding, pregnant, or of childbearing potential; participation in any clinical trial that included any drugs; undergoing treatment with nicotinic acid, renal dialysis, or cancer therapy; anemia; systemic glucocorticoid therapy or use of OAM, ACE inhibitors, or angiotensin II receptor agonists within 30 d; or known allergy to metformin or any TZD drug. Each patient gave written informed consent before entering the trial according to the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the ethical review boards of each participating site before the initiation of the study. There were 15 sites in Hungary and 4 sites in Russia.

Sample size

The sample size was based on the primary objective of demonstrating noninferiority of pioglitazone to metformin in the reduction of A1C from baseline at the primary time point of 32 wk (visit 6). Our criterion for noninferiority was the exclusion of a 0.6% difference between treatments (pioglitazone minus metformin) with a one-sided 95% confidence limit. An *a priori* assumption was made that the common SD would be 1.5% in the change in A1C. It was then determined that a sample size of 80 patients per treatment group would provide at least 80% power to meet our noninferiority criterion. To adjust for the expectation of a 20% dropout rate over the course of 8 months, we randomized 205 patients, 100 to metformin and 105 to pioglitazone.

Statistical methods

The method of analysis of each continuous (as distinguished from categorical) efficacy or safety variable was an analysis of covariance (ANCOVA) of change from baseline to endpoint, and it included only patients who had both a baseline measurement and at least one measurement of the dependent variable during the treatment period. Base-

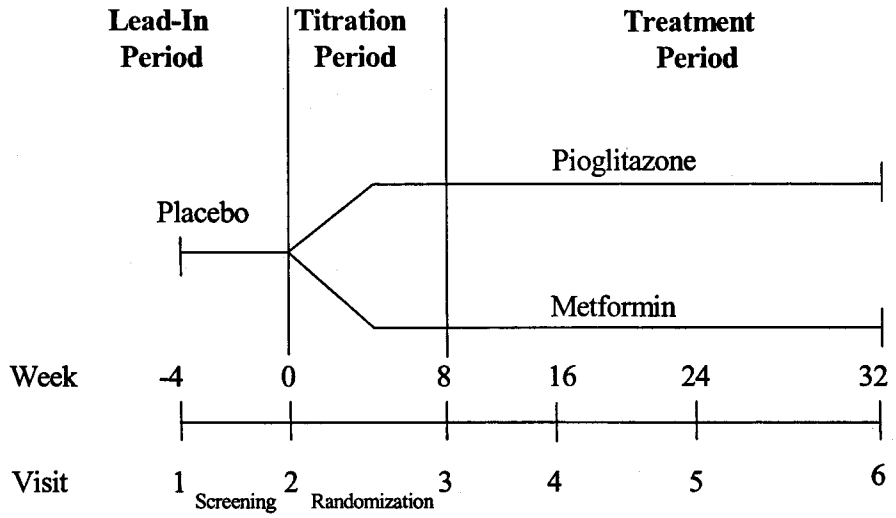

FIG. 1. Study design.

line was defined as the data collected before initiating therapy. All of these analyses were last-observation-carried-forward analyses in which missing values for postbaseline measurements were imputed from the previous nonmissing postbaseline measurement of that variable. The single-slope ANCOVA model included treatment, investigative site, and the baseline value of the dependent variable as explanatory variables. Adjusted (least squares) treatment means were obtained from the model, and the overall test for treatment effect was performed with a significance level of 0.05.

In further exploratory analyses of homeostasis model assessment for insulin sensitivity (HOMA-S), an ANCOVA similar to that described above was performed with change from baseline in HOMA-S as the dependent variable, but with a demographic model that included treatment and investigative site as fixed effects and age, gender, weight at baseline, and baseline HOMA-S as covariates.

Other exploratory analyses of the change from baseline in HOMA-S and the respective relationship to change in A1C were conducted with models that included as explanatory variables treatment, baseline HOMA-S, the change in A1C, and the interaction between change in A1C and treatment.

The analysis of lipoproteins included only patients who were not taking lipid-altering medications or who had no changes in their lipid-altering medications during the study.

Correlation coefficients between efficacy variables were computed using Spearman's method. The comparison between treatments in the analysis of treatment-emergent adverse events (TEAEs) was based on Fisher's exact test. Categorical analyses, such as comparison of incidence of TEAEs, were performed with Fisher's exact test.

Laboratory methods

All laboratory specimens were collected at the participating sites and shipped to a central laboratory (Covance Central Laboratory Services, Geneva, Switzerland). A1C was measured by automated HPLC on the Bio-Rad Variant analyzer (Bio-Rad Laboratories, Inc., Hercules, CA). This method is Diabetes Control and Complications Trial (DCCT) standardized, upper limit of the normal range 6.1%. Additional efficacy measures included FPG and fasting serum insulin (FSI). FPG levels were measured using the hexokinase enzymatic method (Hitachi 747–200 analyzers, Roche Diagnostics, Indianapolis, IN). FSI was measured using microparticle enzyme immunoassay (Abbott IMX, Abbott Laboratories, Abbott Park, IL). Apolipoprotein B (ApoB) was assayed using the Beckman IMMAGE Immunochemistry System (Beckman Coulter, Inc., Palo Alto, CA). Lipoprotein (a) [Lp(a)] assay was performed by automated immunoprecipitin analysis using the SPQ Antibody Reagent Set (DiaSorin, Inc., Stillwater, MN). Serum lipoprotein panels included measurements of TG and cholesterol [total, HDL-C, and low-density lipoprotein cholesterol (LDL-C); routine and Center for Disease Control National Heart, Lung, and Blood Institute Lipid Standardization Program]. HDL-C, LDL-C, and total cholesterol were directly assayed on Hitachi analyzers (Roche Diagnostics, Indianapolis, IN).

Methods for assessment of insulin sensitivity

HOMA-S is derived from measurements of FPG and FSI levels (20). A computer program from the Diabetes Research Laboratories (Oxford, UK) was used to compute HOMA-S instead of using the simple equation for HOMA of insulin resistance (HOMA-IR; Ref. 21).

Safety

Evaluation of safety parameters during the study included measurements of blood pressure (BP), heart rate, body weight, routine blood laboratory parameters, and adverse events. Concomitant medications required by patients were allowed, except those listed in the exclusion criteria.

Results

Of the 321 patients screened for eligibility, 205 patients were assigned for medication randomization at visit 2 (Fig. 2). Baseline anthropometric characteristics and the duration of diabetes from diagnosis to study entry are presented in Table 1. Of the 205 patients (102 males and 103 females) randomly assigned to receive placebo plus pioglitazone (initial dose, 30 mg/d) or placebo plus metformin (initial dose, 850 mg/d), 100 patients (95.2%) in the pioglitazone group and 91 patients (91.9%) in the metformin group completed the 32-wk double-blind treatment period. Seventy-nine patients randomized to pioglitazone were titrated to a final dose of 45 mg/d (77% of group); the mean dose for pioglitazone was 41.5 mg/d. Seventy-two (73%) of those randomized to metformin received a final dose regimen of 2550 mg/d; the mean dose for metformin was 2292 mg/d.

Effects on glycemic control and insulin sensitivity

Both treatment groups had statistically significant reductions from baseline in A1C ($P < 0.0001$ for both treatments), and there was no statistically significant difference between the two groups in A1C change from baseline (Table 2 and Fig. 3). The 95% upper confidence limit for the difference between treatments (pioglitazone minus metformin) of 0.4% met the predefined criterion of the protocol for demonstration of noninferiority of pioglitazone to metformin. Both treatment groups had significant decreases from baseline in FPG ($P < 0.0001$ for both treatments), and there was no statistically significant difference between the treatment groups in FPG change from baseline.

At the 24-wk interim visit, FSI was significantly reduced in both groups by 17.1% ($P < 0.01$) on pioglitazone and 14.9% ($P < 0.05$) on metformin treatment (Fig. 4). The magnitude of reduction was not statistically significantly different between the two groups at this time point. At the endpoint (32 wk) of the study, a significant decrease in FSI was shown in the pioglitazone treatment group ($P < 0.0001$), but the endpoint FSI was not significantly different from baseline in the metformin group (Table 2 and Fig. 4). The results of a combined analysis in which both 24- and 32-wk FSI data points for pioglitazone were considered simultaneously resulted in a 6.2% decrease of serum insulin levels, which is not a significant difference *vs.* baseline ($P = 0.18$). At endpoint, however, the decrease in FSI in the pioglitazone group was significantly different from that of the metformin group ($P < 0.005$).

After 24 wk of treatment, insulin sensitivity (as assessed by HOMA-S) increased significantly in the pioglitazone group (17.4%; $P < 0.05$) as compared with an increase of 8.9% in the metformin group ($P = 0.21$; Fig. 4). At this stage of the study (24 wk), the difference between treatment groups was not statistically significant. At study endpoint, however, the HOMA-S increase was maintained in the pioglitazone group (14.9%; $P < 0.005$), but there was no difference compared with baseline level in the metformin group (−0.9%; $P = 0.87$). There was a statistically significant difference between the treatment groups in favor of pioglitazone in increasing insulin sensitivity as assessed by HOMA-S ($P < 0.005$; Table 2 and Fig. 4) at the 32-wk study endpoint. Further analysis of HOMA-S using logarithmically transformed results confirmed the statistically significant difference ($P < 0.005$) between treatments in the change from baseline. In a multivariate model including baseline HOMA-S, baseline body weight, age, gender, and clinical center as covariates, the differences between treatments in the change

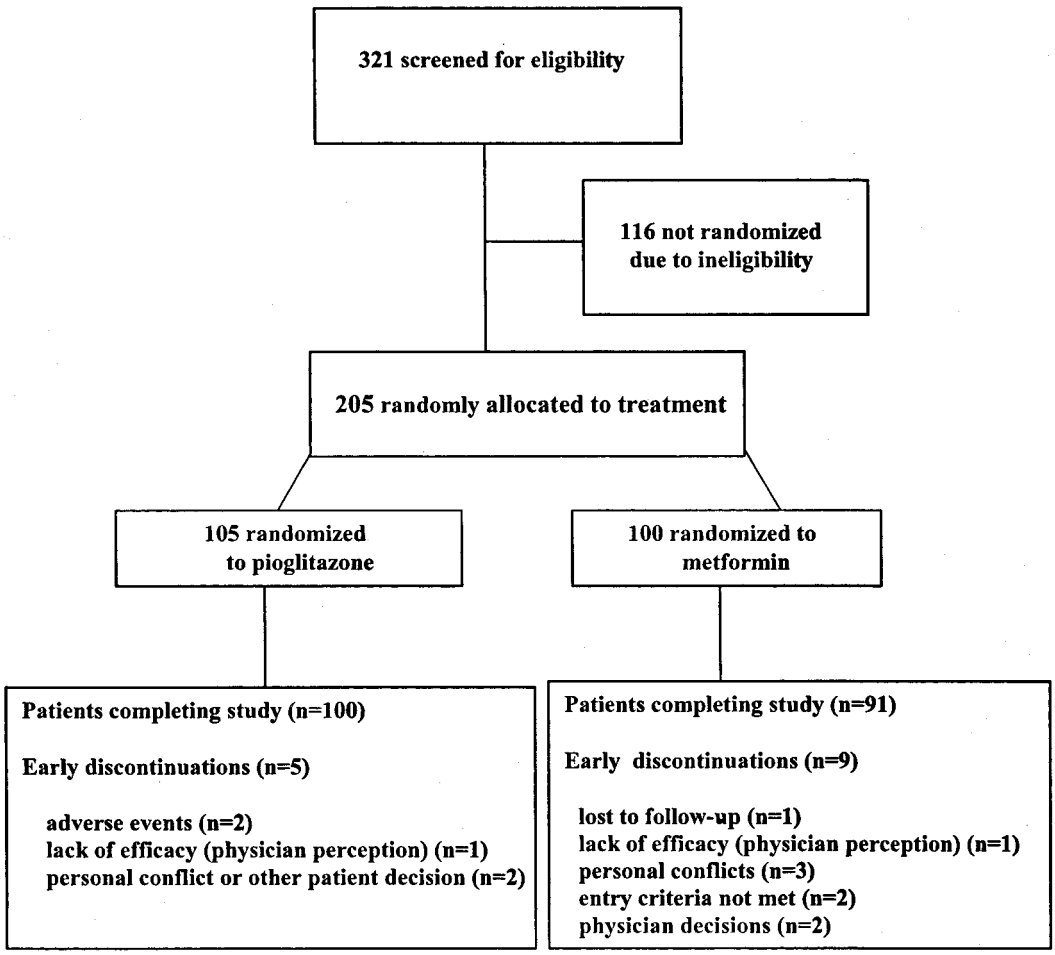

FIG. 2. Patient enrollment and follow-up.

TABLE 1. Patient baseline characteristics

Variables	Pioglitazone (n = 105)	Metformin (n = 100)
Age (yr)	54.2 ± 9.1	55.8 ± 8.4
Gender (F/M) (%)	56.2/43.8	44.0/56.0
Weight (kg)	86.6 ± 15.6	88.9 ± 15.9
BMI (kg/m^2)	31.3 ± 4.2	31.1 ± 4.4
Duration of diabetes (months)	5.6 ± 3.8	6.3 ± 3.9

Data are mean ± SD, except gender. Mean values were not significantly different between patient groups. F, Female; M, male; BMI, body mass index.

in HOMA-S were also more pronounced with pioglitazone therapy (mean treatment difference, 16.37; SD, 6.77; $P < 0.05$ for the difference between treatment groups). Despite the marked effect of pioglitazone therapy on both A1C and HOMA-S, the correlation between the changes was not significant (r = 0.08).

Effects on lipoproteins

Both pioglitazone and metformin treatment produced statistically significant increases in HDL-C (0.22 mmol/liter and 0.13 mmol/liter, respectively; $P < 0.0001$ *vs.* baseline). The effect on HDL-C levels, however, was significantly greater in the pioglitazone group compared with metformin ($P = 0.02$). LDL-C in the metformin group decreased significantly compared with both baseline (−0.18 mmol/liter; $P = 0.04$) and the pioglitazone group ($P = 0.003$), in which the increase in LDL-C (0.16 mmol/liter) was not statistically significant ($P = 0.055$). Total cholesterol was unchanged in the pioglitazone group but decreased significantly in the metformin group compared with both baseline (−0.37 mmol/liter; $P = 0.002$) and the pioglitazone group ($P = 0.02$). A significant increase in Lp(a) was observed with pioglitazone (0.02 g/liter; $P = 0.003$); no significant change was observed with metformin. Both therapies significantly reduced TG levels (−0.91 mmol/liter for pioglitazone, $P = 0.001$; and −0.63 mmol/liter for metformin, $P = 0.03$). The LDL-C/ApoB ratio increased significantly in the pioglitazone treatment group compared with both baseline (0.25; $P < 0.0001$) and with metformin treatment ($P < 0.0001$), whereas this ratio remained unchanged in the metformin group.

Safety

Heart rate was not influenced by either of the OAM therapies. The systolic BP, as well as the diastolic BP, was significantly reduced in both treatment arms (Table 3). Patients on pioglitazone experienced slight weight gain (0.7 kg), whereas those on metformin lost weight (−2.4 kg; Table 3).

A significant decrease in liver enzymes (ALT and AST) was observed on pioglitazone treatment, whereas liver en-

TABLE 2. Changes from baseline to endpoint for glycemic efficacy variables

	Pioglitazone			Metformin			Pioglitazone *vs.* metformin
	Baseline	Change from baseline	*P*	Baseline	Change from baseline	*P*	*P*
A1C (%)	8.6	−1.3	<0.0001	8.6	−1.5	<0.0001	0.280
FPG (mmol/liter)	11.8	−3.0	<0.0001	12.4	−2.8	<0.0001	0.620
FSI (pmol/liter)	101.2	−22.7	<0.0001	118.3	−1.3	0.803	0.003
HOMA-S (%)	69.1	14.9	0.002	66.7	−0.9	0.867	0.020

Data represent mean absolute change from baseline.

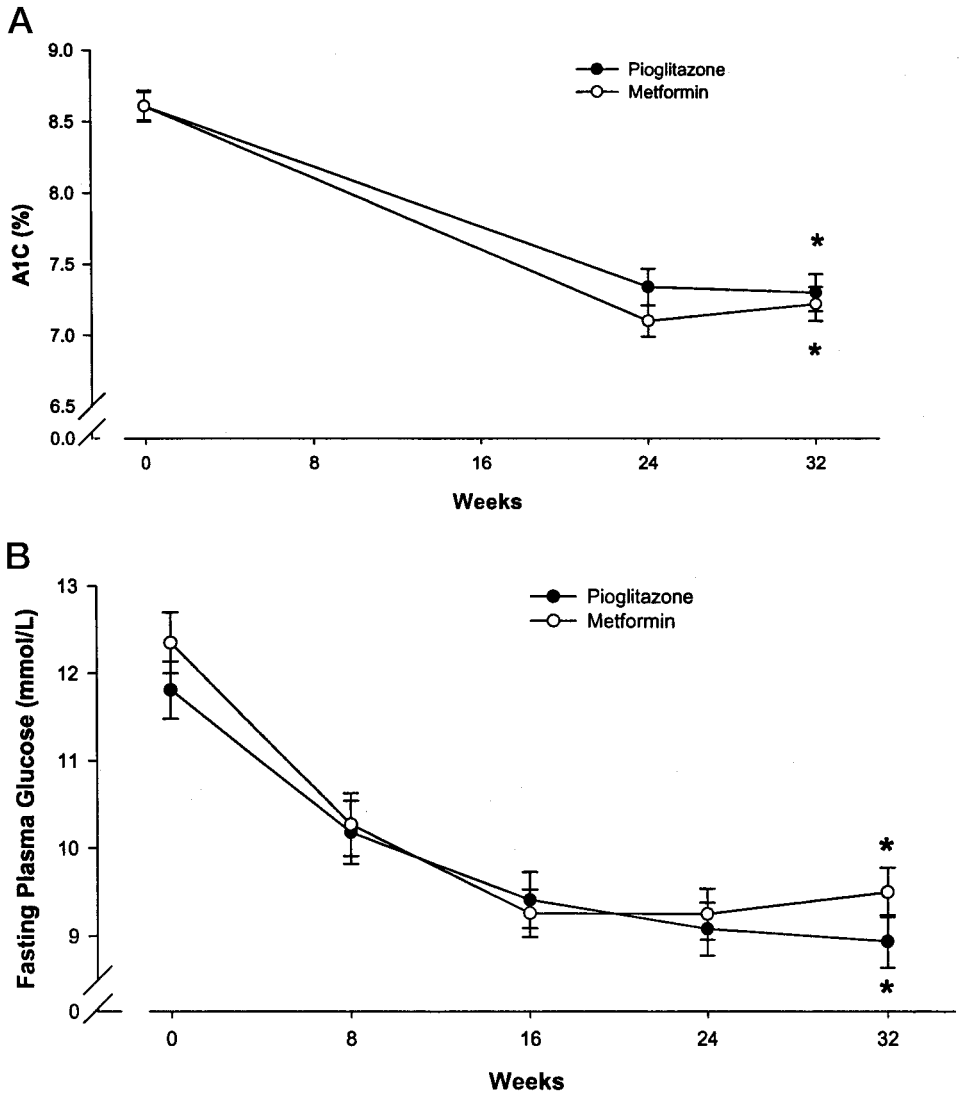

FIG. 3. A, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on A1C. *, $P < 0.0001$ *vs.* baseline. B, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on fasting plasma glucose. *, $P < 0.0001$ *vs.* baseline.

zymes remained unchanged on metformin therapy (Table 3). In further analyses of the liver enzymes, the subset of patients with baseline values above the upper limit of the normal range (n = 16 and n = 21 for pioglitazone and metformin, respectively) was analyzed for change from baseline. The decrease in ALT was statistically significant for pioglitazone ($P = 0.001$), but not for metformin. There was a statistically significant difference between the treatment groups ($P = 0.014$) in favor of pioglitazone in this subset of patients. For patients with AST above the upper limit of the normal range (n = 12 and n = 6 for pioglitazone and metformin, respectively), the pioglitazone group had a significant decrease from baseline ($P = 0.035$). The difference in the decrease in AST between the two treatment groups was 14.5 U/liter in favor of pioglitazone, but was not statistically significant.

Both pioglitazone and metformin were well tolerated. Five (4.8%) patients treated with pioglitazone and nine (9%) patients treated with metformin discontinued therapy before the end of the study. Two patients in the pioglitazone group discontinued due to an adverse event (Fig. 2). Neither of the two adverse events, which included cholecystitis and chest pain, were drug-related. Overall TEAE incidence was 51.4%

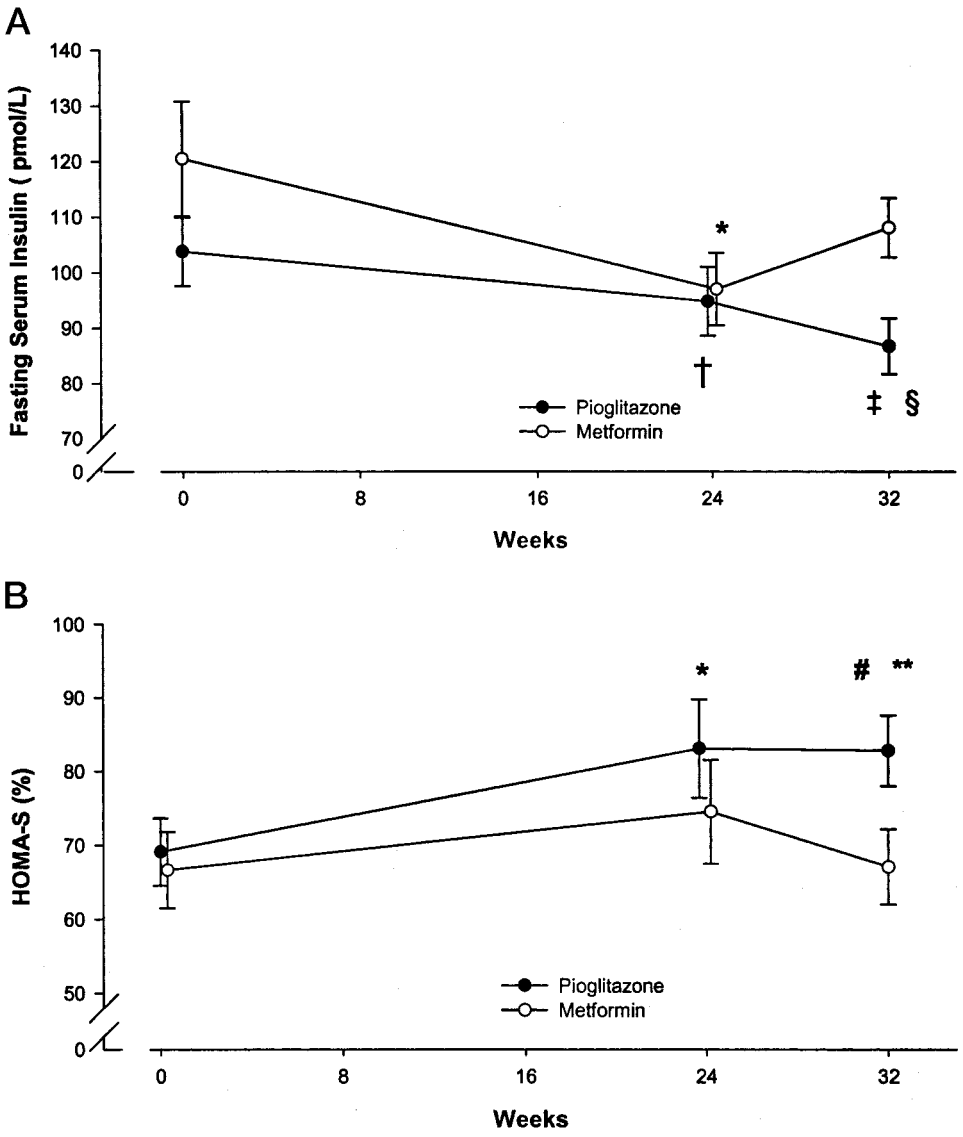

FIG. 4. A, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on fasting serum insulin. B, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on HOMA-S. Values represent mean ± SEM. *, $P < 0.05$ *vs.* baseline; †, $P < 0.01$ *vs.* baseline; ‡, $P < 0.0001$ *vs.* baseline; §, $P < 0.005$ *vs.* metformin; #, $P < 0.005$ *vs.* baseline; **, $P < 0.05$ *vs.* metformin.

TABLE 3. Changes from baseline for body weight, BP, and liver function values

	Pioglitazone			Metformin			Pioglitazone *vs.* metformin
	Baseline	Change from baseline	*P*	Baseline	Change from baseline	*P*	*P*
Body weight (kg)	86.1	0.7 ± 0.4	0.041	88.8	−2.4 ± 0.4	<0.0001	<0.0001
Systolic BP	140.1 ± 15.4	−6.2 ± 1.2	<0.0001	142.6 ± 14.2	−6.7 ± 1.2	<0.0001	0.774
Diastolic BP	87.0 ± 8.5	−3.9 ± 0.6	<0.0001	88.0 ± 8.2	−3.9 ± 0.6	<0.0001	0.979
ALT (U/liter)	30.3	−6.8 ± 1.6	<0.0001	29.0	1.2 ± 1.6	0.463	0.0002
AST (U/liter)	24.2	−2.2 ± 0.9	0.011	22.6	0.7 ± 0.9	0.464	0.016

Data represent changes from baseline ± SEM.

on pioglitazone and 47.0% on metformin ($P = 0.577$). TEAEs reported in more than 5% of the patients were headache, diarrhea, lower-limb edema, nausea, and influenza, with no difference between treatments in headache, nausea, and influenza. Diarrhea was significantly more frequently reported in the metformin group (16% *vs.* 3%; $P = 0.001$) whereas lower limb edema was more frequently reported in the pioglitazone treatment group (12.4% *vs.* 4%; $P = 0.041$).

Discussion

As the primary outcome of this prospective double-blind, randomized clinical trial comparing OAM monotherapy with pioglitazone to metformin, a similar efficacy was found in the reduction of A1C and FPG in patients with recently diagnosed type 2 diabetes who were also OAM-naive. These data are in agreement with observations from previous stud-

ies in which other TZDs and metformin were equally effective in glucose control when added to ongoing OAM therapy or when used to replace another OAM (22, 23). These studies, however, were not powered to detect small differences in glycemic control. A recent study involving approximately 30 patients per treatment arm has demonstrated that a maximal dose of troglitazone was superior in improving glycemic control as compared with a maximal dose of metformin (24). Because comparator OAMs were added to ongoing insulin therapy in the Strowig *et al.* (24) study and insulin therapy was not a component of our study, however, a direct comparison of the data is not feasible.

The improvement in glycemic control noted in pioglitazone-treated patients in the current trial was associated with enhancement of HOMA-S, an indicator of insulin sensitivity (reduction of insulin resistance), whereas no significant effect on this parameter was observed with metformin treatment in our study population. FSI was significantly reduced in both groups after 24 wk of treatment [−17.1% in the pioglitazone group ($P < 0.01$); −14.9% in the metformin group ($P < 0.05$)]. At the study endpoint (32 wk), FSI remained significantly reduced in the pioglitazone group ($P < 0.0001$), whereas FSI was not significantly different from baseline in the metformin group ($P = 0.80$). Further investigation, in which both 24- and 32-wk FSI data points for pioglitazone were considered simultaneously, resulted in a 6.2% decrease of serum insulin levels which, although not significantly different from baseline ($P = 0.18$), suggests a decreasing trend. This finding, an absence of consistent measurements of improved insulin sensitivity with metformin therapy, is in conflict with previous studies that have shown improvements in insulin sensitivity with metformin as compared with TZDs, as assessed by the hyperinsulinemic-euglycemic clamp technique (22, 23, 25, 26). Indeed, metformin does appear to improve peripheral glucose disposal by an increase in AMP-activated protein kinase activity (27). The lack of observed effect on insulin sensitivity with metformin treatment in the current study may be attributable to the limitations of HOMA-S assessment to detect small changes in insulin sensitivity. HOMA-S is applicable primarily in studies involving larger sample sizes and is not powered to detect small differences. Lesser changes within treatment groups (as might be expected with metformin therapy) were not detectable with the sample size used for this study. The lack of detection of a significant improvement in HOMA-S in the metformin group could also be related to the characteristics of the patient population in the current study, *i.e.* OAM-naive, newly diagnosed patients with type 2 diabetes. In a similar population, rosiglitazone (another TZD), but not metformin, enhanced both insulin- and exercise-stimulated glucose uptake (28). Another study involving OAM-naive patients also failed to demonstrate increased insulin sensitivity with metformin, as assessed using the hyperinsulinemic clamp method (29). This evidence, combined with the current findings, raises the possibility of a more limited enhancement of peripheral insulin sensitivity with metformin monotherapy in drug-naive patients in contrast to results of studies in which metformin was added to ongoing OAM or insulin treatment (22, 23, 25, 26). Further investigation is indicated to substantiate this hypothesis.

The present study clearly shows a difference in HOMA-S and FSI between treatment groups (in favor of pioglitazone). Furthermore, the significant difference between HOMA-S results for the two drugs in the current study is in accordance with a glucose disposal rate for troglitazone that is two to four times higher than that observed with metformin, as measured using the same clamp techniques used in the previously cited studies (22, 23, 25, 26).

Both metformin and pioglitazone have been shown to improve glycemic control as well as insulin resistance; therefore a direct comparison of these two drugs is of particular clinical interest. Pioglitazone is a thiazolidinedione, and this class of drugs has been shown to improve glycemic control primarily by increasing peripheral insulin sensitivity in patients with type 2 diabetes (30), whereas metformin, a biguanide, exerts its effect primarily in the liver by decreasing hepatic glucose output (14–17). This is the first head-to-head comparison of the effects of pioglitazone and metformin, and, together with the recent publication of Hällsten *et al.* (28), is one of the first trials to compare the effects of TZD and metformin monotherapy both in general and specifically in patients at early stages of type 2 diabetes who are also naive to glucose-lowering medication. Because insulin resistance prevails in these patients, insulin-sensitizing agents represent viable treatment options (5).

Both treatments were generally well tolerated. Hepatic function in type 2 diabetes is of particular interest. Mean levels of serum ALT and AST decreased in the pioglitazone-treated patients compared with baseline and with the metformin group. A recent study has shown that pioglitazone decreased hepatic fat content in patients with type 2 diabetes, and this decrease correlated with enhanced hepatic insulin sensitivity (31). Our finding reinforces the hepatic safety of pioglitazone as well as metformin in patients with early stages of type 2 diabetes. In addition to different effects on insulin sensitivity, pioglitazone and metformin had different effects on body weight; pioglitazone treatment resulted in weight gain, whereas metformin treatment resulted in weight loss. Weight reduction in patients treated with metformin has been shown in a vast majority of previous studies (15, 17, 32). Because obesity often contributes to the etiology of type 2 diabetes, weight reduction with metformin therapy may be an additional benefit. Weight loss in patients who are obese may be particularly beneficial in terms of the associated risk reduction of both microvascular and macrovascular complications, as correlated with metformin treatment in the UKPDS study analysis (18). More consistently, increased body weight has been reported after treatment with PPAR-γ agonists in general (5, 7–11). Mean weight gain with pioglitazone was minimal in the present study (0.7 kg, or 0.9%, over 8 months) and markedly lower than the 5% average increase in body weight previously observed in other trials with pioglitazone, suggesting that weight gain may be less pronounced in drug-naive patients and early stages of the disease, or both. An evaluation of the clinical significance of treatment-induced weight gain must include consideration of the following: the size of the gain; the quality of newly acquired weight, that is, whether weight gain is a consequence of increased adipose tissue, lean body mass, or fluid retention; and, if adipose tissue is involved, how the addi-

tional fat is distributed. Previous studies have shown a shift of fat distribution from visceral to sc adipose tissue during treatment with thiazolidinediones, including pioglitazone (11, 33), suggesting this shift as a potential explanation for the seemingly paradoxical simultaneous improvement in glycemia and insulin resistance observed with increase in body weight (34). Because visceral adiposity was not assessed in the present study, we could not determine whether relationships existed between body fat distribution and the differential effects of pioglitazone and metformin on glycemic control and insulin sensitivity.

The lipid profiles of OAM-naive patients who receive either pioglitazone or metformin reveal common trends as well as differences. A strong association between low HDL-C levels or elevated TG levels and the higher risk of coronary heart disease in patients with diabetes is well established (35–38). Improvements were noted in these lipid parameters with both pioglitazone and metformin. Although both treatment groups displayed significant increases in HDL-C levels, however, a greater effect was observed with pioglitazone treatment. An ability to significantly increase HDL-C levels appears to be the primary lipid effect observed with pioglitazone treatment, as supported by findings in this and previous studies (13, 39–41). Metformin had been previously shown to decrease LDL-C (32), and this may contribute to the absence of change in total cholesterol in this group. The absence of a significant change in LDL-C combined with the greater increase in HDL-C accounts for the increase in total cholesterol observed in the pioglitazone group. Both pioglitazone and metformin therapies significantly reduced TG levels. There was a significant increase in the LDL-C/ApoB ratio in the pioglitazone group compared both with baseline and with the metformin group, for which there was no change in the LDL-C/ApoB ratio. No change in Lp(a) levels was observed with metformin therapy, whereas Lp(a) levels were increased with pioglitazone therapy, a finding previously reported for troglitazone (42). In contrast, another previous study concluded that pioglitazone had no effect on Lp(a) (40). Further studies are indicated to clarify divergent effects on Lp(a) in different patient populations with pioglitazone therapy, and whether or not the Lp(a) increase is a class effect of the TZDs.

Blood pressure, as a safety outcome measure, was reduced by both treatments in the present study. It has been suggested that a reduction of BP by TZDs may be related to the reduction of insulin resistance and to direct vasoprotective effects (5). This is also consistent with findings in animal experiments (43) and clinical observations with other TZDs (44).

Limitations of this study include the use of indirect measures of insulin sensitivity as indicators of insulin resistance, instead of more invasive and logistically challenging techniques, such as the hyperinsulinemic-euglycemic clamp, or a frequently sampled iv glucose tolerance test. Indeed, in elderly patients (mean age, 73 yr) with poorly controlled type 2 diabetes, HOMA-IR did not correlate with the direct measurement; in younger patients (mean age, 55 yr), similar in age to those investigated in the current study, however, HOMA-IR was found to correlate with direct measurements of insulin sensitivity (45). A strong correlation between HOMA and clamp results has also been demonstrated in other studies involving patients with type 2 diabetes (46). Quon (47) has emphasized greater clinical utility of HOMA as compared with less predictive indirect measures of insulin sensitivity such as the fasting glucose to insulin ratio, especially when glucose levels are abnormal. Based on the ability of HOMA to accurately mimic the results of glucose clamp techniques, Bonora *et al.* (48) have concluded that HOMA is a reliable indicator of insulin sensitivity in large-scale studies (such as the present trial) in which procedures such as clamp techniques may be impractical. Thus, the indirect measures of insulin sensitivity used in this study are considered as surrogates for insulin resistance measured using the diagnostic gold standard of clamp studies.

Results of our study confirm that both pioglitazone and metformin represent effective and safe first-line pharmacological treatment options in recently diagnosed, OAM-naive patients with type 2 diabetes. The present study demonstrates that pioglitazone and metformin monotherapies are equally effective in lowering A1C and FPG, but improvements in indicators of insulin sensitivity (as demonstrated by increases in HOMA-S and reductions in FSI) were more pronounced in patients on pioglitazone therapy. Further clinical investigations are indicated to clarify to what degree insulin sensitivity contributes to the efficacy of pioglitazone or metformin monotherapy in the early stages of type 2 diabetes.

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