

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

IMRE PAVO, GYÖRGY JERMENDY, TAMAS T. VARKONYI, ZSUZSA KERENYI, ANDRAS GYIMESI, SERGEJ SHOUSTOV, MARINA SHESTAKOVA, MATTHIAS HERZ, DON JOHNS, BELINDA J. SCHLUCHTER, ANDREAS FESTA, AND MENG H. TAN

Lilly Research Laboratories (I.P., M.H., D.J., B.J.S., A.F., M.H.T.), Eli Lilly & Company, Indianapolis, Indiana 46201; Bajcsy-Zsilinszky Hospital (G.J.), Budapest H-1106, Hungary; Medical School (T.T.V.), University of Szeged, Szeged H-6725, Hungary; St. Imre Hospital (Z.K.), Budapest H-1115, Hungary; Pandy Kalman Hospital (A.G.), Gyula H-5700, Hungary; Medical Military Academy (S.S.), Saint Petersburg, Russia 191186; and Endocrinology Research Center (M.S.), Moscow, Russia 117036

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 mea-

sured by hemoglobin A1C and fasting plasma glucose. At end-point, 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 ele-

vated 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-naïve 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 medi-

cation 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/m²; 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-

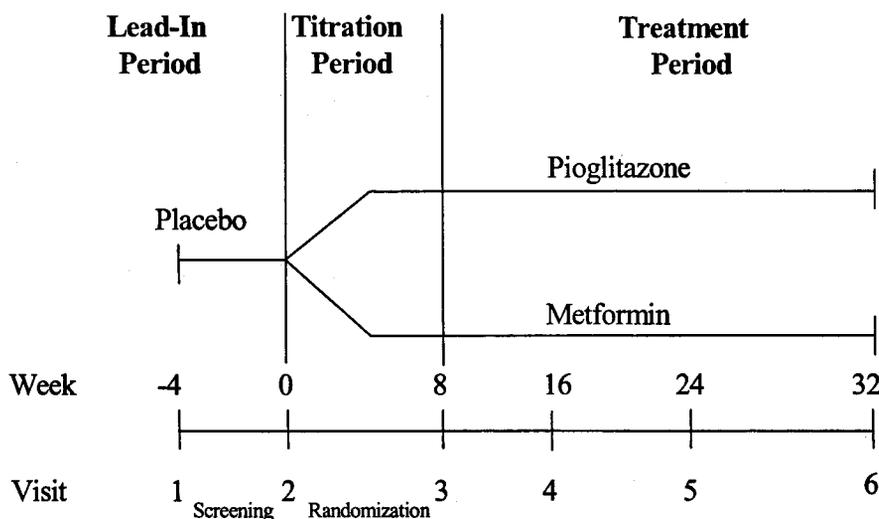


FIG. 1. Study design.

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 (Dia-Sorin, 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

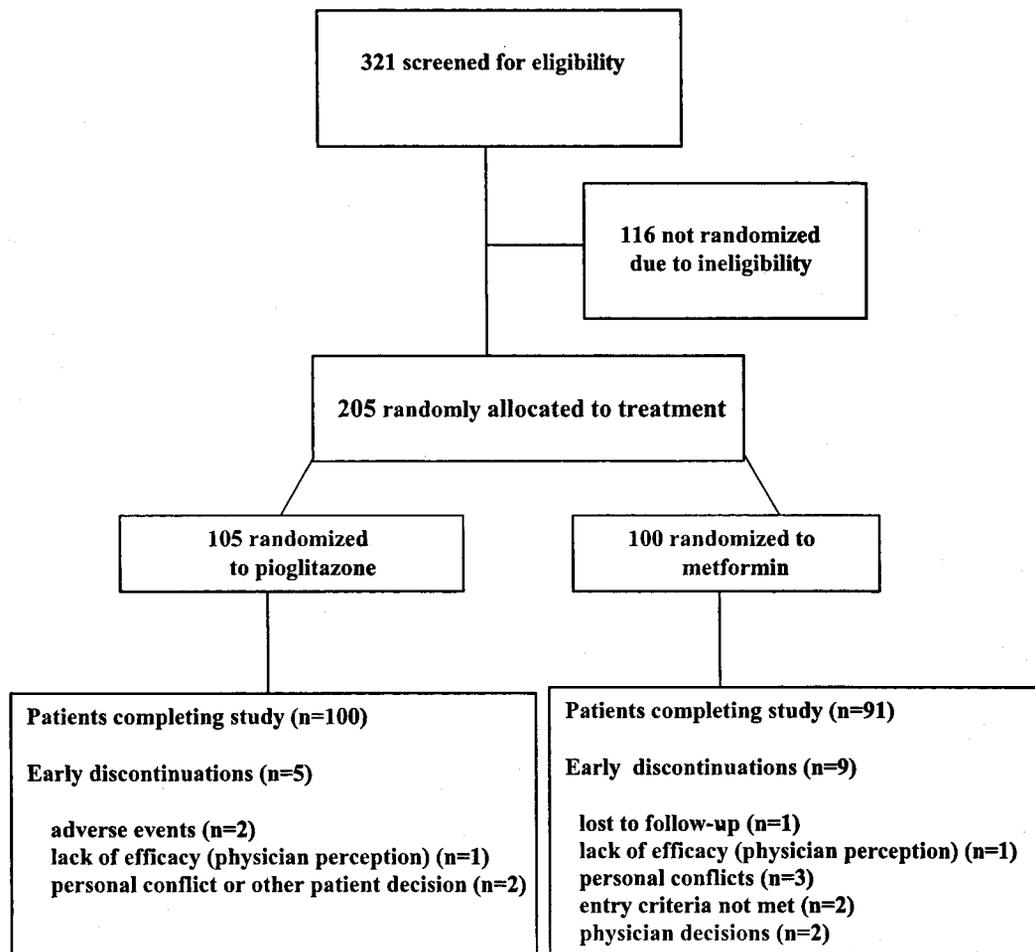


FIG. 2. Patient enrollment and follow-up.

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 com-

pared 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 glyceic efficacy variables

| | Pioglitazone | | | Metformin | | | Pioglitazone vs. metformin |
|------------------|--------------|----------------------|----------|-----------|----------------------|----------|----------------------------|
| | Baseline | Change from baseline | <i>P</i> | Baseline | Change from baseline | <i>P</i> | <i>P</i> |
| 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.

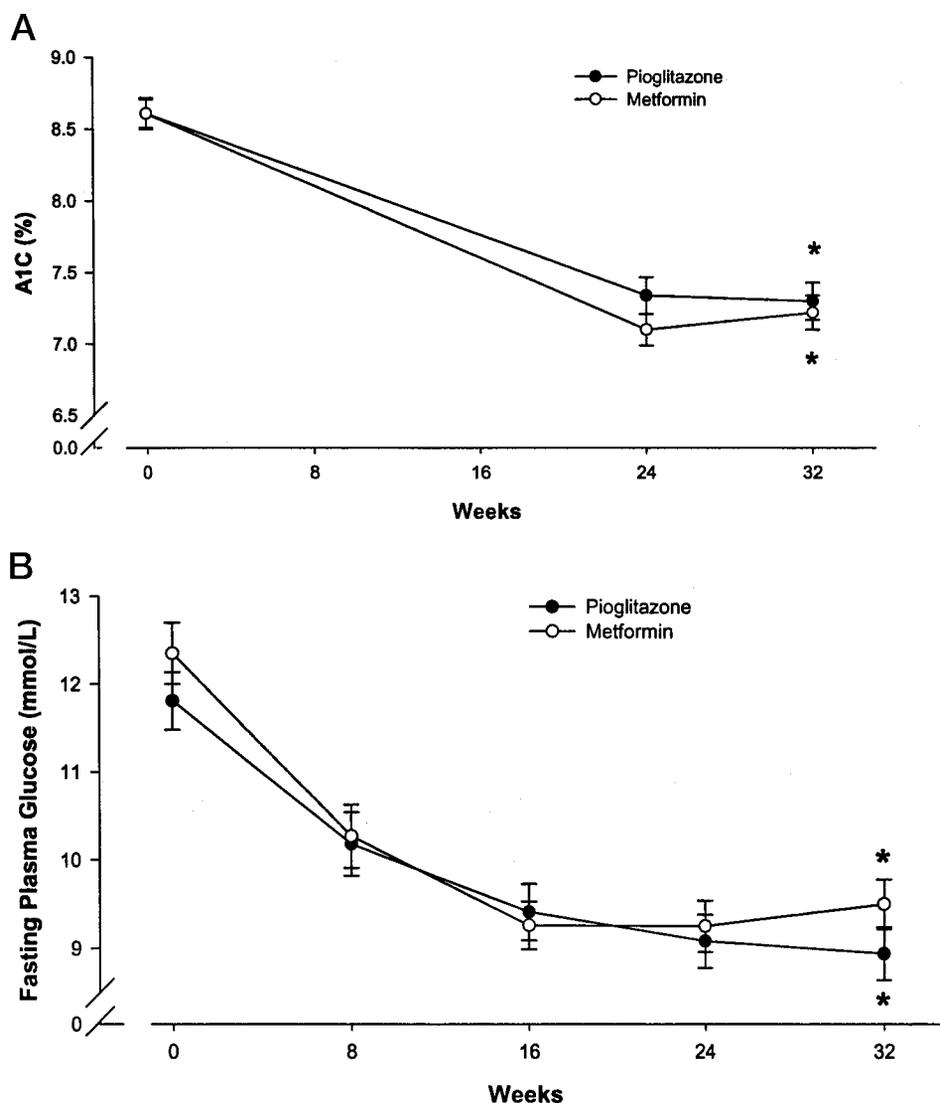


FIG. 3. A, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on A1C. *, $P < 0.0001$ vs. baseline. B, Effects of pioglitazone (up to 45 mg/d) and metformin (up to 2550 mg/d) treatment on fasting plasma glucose. *, $P < 0.0001$ vs. baseline.

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, respec-

tively), 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 \pm 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.

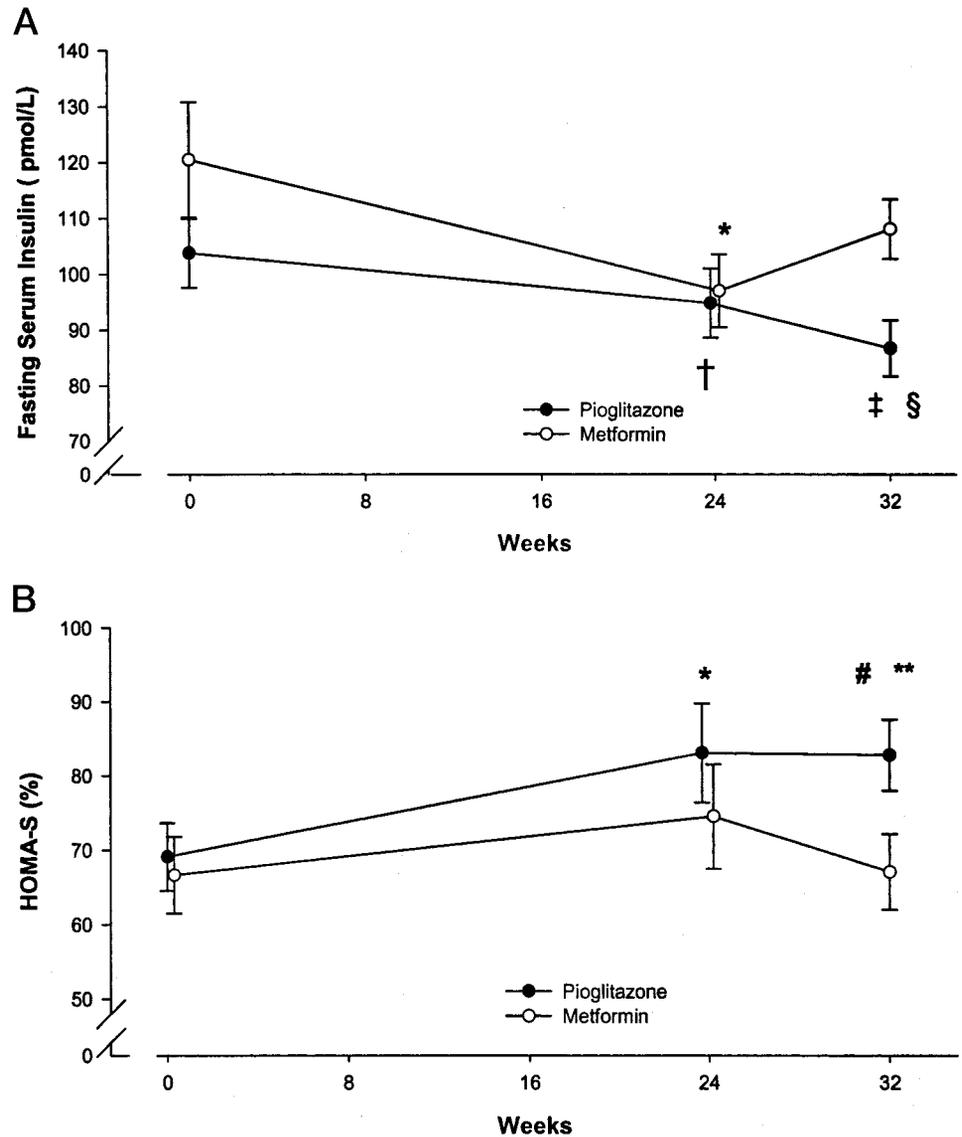


TABLE 3. Changes from baseline for body weight, BP, and liver function values

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

Data represent changes from baseline \pm 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.

Acknowledgments

Appreciation is expressed to the following members of the H6E-MC-GLAE Study Group. In Hungary: Adrás Bruncsák, Bács-Kiskun County Hospital, Kecskemét; Tamás Czifány, Elisabeth Hospital, Jászberény; Erzsébet Dömötör, Máv Korház, Budapest; Csaba Farsang and Zsuzsa Kerényi, Saint Imre's Hospital of Budapest Council, Budapest; József Fövényi, Hospital of Budapest Council on the Péterfy Sándor Street, Budapest; András Gyimesi, Pándy Kálmán Hospital, Gyula; Tibor Hidvégi, Petz Aladár County Hospital, Győr; György Jermendy, Bajcsy-Zsilinszky Hospital, Budapest; Judit Nagy, Pécs University, Pécs; Gábor Nyirati, City Hospital of Baja, Baja; Tamás Oroszlán, Zala County Hospital, Zalaegerszeg; János Vadász, Hetényi Géza Hospital, Szolnok; Gyöző Vándorfi, Veszprém County Csolnoky Ferenc Hospital, Veszprém; and Tamás Várkonyi, University of Szeged, Szeged. In Russia: Irina Demidova, Moscow Medical Academy, Moscow; Marina V. Shestakova and Olga M. Smirnova, Endocrinological Research Center, Moscow; and Sergej Shoustov, Medical Military Academy, Saint Petersburg.

Appreciation is also expressed to Claudia Kriebaum, Noemi Jurida, Larissa Tsibina, and Petra Ficenc for coordinating this study and to Margaret A. Campbell, J. David Oakley, and Pamela P. Erickson for extensive technical and editorial assistance with this manuscript.

Received November 13, 2002. Accepted January 21, 2003.

Address all correspondence and requests for reprints to: Imre Pavo, M.D., Ph.D., Lilly Research Laboratories, Lilly Corporate Center, Drop Code 2130, Indianapolis, Indiana 46285. E-mail: pavo_imre@lilly.com.

A portion of these data were presented at the 38th Annual Meeting of the European Association for the Study of Diabetes, Budapest, Hungary, 2002 [Diabetologia 45(Suppl 2):250 (Abstract 779) and 251-2 (Abstract 783)].

References

1. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR 1992 Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25 year follow-up study. *Lancet* 340:925–929
2. Reaven GM 1996 Insulin resistance and its consequences: non-insulin dependent diabetes mellitus and coronary heart disease. In: LeRoith D, Taylor SE, Olefsky JM, eds. *Diabetes mellitus*. Philadelphia: Lippincott-Raven; 509–519

3. **UK Prospective Diabetes Study Group (UKPDS 33)** 1998 Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352:837–853
4. **UK Prospective Diabetes Study Group (UKPDS 38)** 1998 Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. *Br Med J* 317:703–713
5. **Martens FMAC, Visseren FLJ, Lemay J, de Koning EJP, Rabelink TJ** 2002 Metabolic and additional vascular effects of thiazolidinediones. *Drugs* 62:1463–1480
6. **Mudaliar S, Henry RR** 2002 PPAR agonists in health and disease: a pathophysiologic and clinical overview. *Curr Opin Endocrinol Diabetes* 9:285–302
7. **Fonseca VA, Valiquett TR, Huang SM, Ghazzi MN, Whitcomb RW** 1998 Troglitazone monotherapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled study. *The Troglitazone Study Group. J Clin Endocrinol Metab* 83:3169–3176
8. **Prigeon RL, Kahn SE, Porte Jr D** 1998 Effect of troglitazone on B cell function, insulin sensitivity, and glycemic control in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 83:819–823
9. **Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI** 2001 The Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 86:280–288
10. **Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino LJ, DeFronzo RA** 2001 Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 24:710–719
11. **Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA** 2002 Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 87:2784–2791
12. **Miyazaki Y, Matsuda M, DeFronzo RA** 2002 Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. *Diabetes Care* 25:517–523
13. **Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE** 2001 The impact of pioglitazone on glycemic control and atherogenic dyslipidemia inpatients with type 2 diabetes mellitus. *Coron Artery Dis* 12:413–423.
14. **De Fronzo RA, Barzilai N, Simonson DC** 1991 Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 73:1294–1301
15. **Bailey CJ, Turner RC** 1996 Drug therapy: metformin. *N Engl J Med* 334:574–579
16. **Cusi K, Consoli A, DeFronzo RA** 1996 Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 81:4059–4067
17. **Cusi K, DeFronzo RA** 1998 Metformin: a review of its metabolic effects. *Diabetes Rev* 6:89–131
18. **UK Prospective Diabetes Study Group (UKPDS 34)** 1998 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet* 352:854–865
19. **Bennett PH** 1999 Impact of the new WHO classification and diagnostic criteria. *Diabetes Obes Metab* 1(Suppl 2):S1–S6
20. **Matthews DR, Hosker JP, Redunski AS, Naylor BA, Treacher DF, Turner RL** 1985 Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419
21. **Levy JC, Matthews DR, Hermans MP** 1998 Correct homeostasis model assessment (HOMA) uses the computer program. *Diabetes Care* 21:2191–2192
22. **Chu NV, Kong AP, Kim DD, Armstrong D, Baxi S, Deutsch R, Caulfield M, Mudaliar SR, Reitz R, Henry RR, Reaven PD** 2002 Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care* 25:542–549
23. **Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI** 1998 Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867–872
24. **Strowig SM, Aviles-Santa ML, Raskin P** 2002 Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in type 2 diabetes. *Diabetes Care* 25:1691–1698
25. **Kim YB, Ciaraldi TP, Kong A, Kim D, Chu N, Mohideen P, Mudaliar S, Henry RR, Kahn BB** 2002 Troglitazone but not metformin restores insulin-stimulated phosphoinositide 3-kinase activity and increases p110 β protein levels in skeletal muscle of type 2 diabetic subjects. *Diabetes* 51:443–448
26. **Ciaraldi TP, Kong APS, Chu NV, Kim DD, Baxi S, Loviscach M, Plodkowski R, Reitz R, Caulfield M, Mudaliar S, Henry RR** 2002 Regulation of glucose transport and insulin signaling by troglitazone or metformin in adipose tissue of type 2 diabetic subjects. *Diabetes* 51:30–36
27. **Musi N, Hirshman MF, Nygren J, Svanfeldt M, Bavenholm P, Rooyackers O, Zhou G, Williamson JM, Ljunqvist O, Efendic S, Moller DE, Thorell A, Goodyear LJ** 2002 Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. *Diabetes* 51:2074–2081
28. **Hällsten K, Virtanen KA, Lönnqvist F, Sipilä H, Oksanen A, Viljanen T, Rönnemaa T, Viikari J, Knuuti J, Nuutila P** 2002 Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. *Diabetes* 51:3479–3485
29. **Wu MS, Johnston P, Sheu WH-H, Hollenbeck CB, Jeng C-Y, Goldfine ID, Chen Y-DI, Reaven GM** 1990 Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 13:1–8
30. **Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, Inzucchi S, Kelley D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI** 1998 Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 128:176–185
31. **Bajaj M, Suraamornkul S, Pratipanawatr T, Hardies L, Glass L, Miyazaki Y, Pratipanawatr W, Cersosimo E, DeFronzo R** 2002 Effect of pioglitazone on splanchnic glucose uptake, endogenous glucose production, and hepatic fat content in type 2 diabetes mellitus (T2DM). *Diabetes* 51(Suppl 2):A35 (Abstract 141)
32. **DeFronzo RA, Goodman AM** 1995 Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *The Multicenter Metformin Study Group. New Engl J Med* 333:541–549
33. **Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, Tajima N, Ikeda Y** 1999 Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 22:908–912
34. **Fonseca V, Foyt HL, Shen K, Whitcomb R** 2000 Long-term effects of troglitazone: open-label extension studies in type 2 diabetic patients. *Diabetes Care* 23:354–359
35. **Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA** 1990 Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 322:1700–1707
36. **Gordon DJ, Rifkind BM** 1989 High-density lipoprotein: the clinical implications of recent studies. *N Engl J Med* 321:1311–1316
37. **Goldbourt U, Yaari S, Medalie JH** 1997 Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality: a 21-year follow-up of 8000 men. *Atheroscler Thromb Vasc Biol* 17:107–113
38. **Lehto S, Ronnema T, Haffner SM, Pyörälä K, Kallio V, Laakso M** 1997 Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 46:1354–1359
39. **Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL** 2000 Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *The Pioglitazone 001 Study Group. Diabetes Care* 23:1605–1611
40. **Nagai Y, Abe T, Nomura G** 2001 Does pioglitazone, like troglitazone, increase serum levels of lipoprotein(a) in diabetic patients? *Diabetes Care* 24:408–409
41. **Khan MA, St. Peter JV, Xue JL** 2002 A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 25:708–711
42. **Tack CJ, Smits P, DeMacker PN, Stalenhoef AF** 1999 Effect of troglitazone on lipoprotein(a) levels in obese subjects. *Diabetes Care* 22:1752–1753
43. **Kaufman LN, Peterson MM, DeGrange LM** 1995 Pioglitazone attenuates diet-induced hypertension in rats. *Metabolism* 44:1105–1109
44. **Ogihara T, Rakugi H, Ikegami H, Mikami H, Masuo K** 1995 Enhancement of insulin sensitivity by troglitazone lowers blood pressure in diabetic hypertensives. *Am J Hypertens* 8:316–320
45. **Katsuki A, Sumida Y, Urakawa H, Gabazza EC, Murashima S, Morioka K, Kitagawa N, Tanaka T, Araki-Sasaki R, Hori Y, Nakatani K, Yano Y, Adachi Y** 2002 Neither homeostasis model assessment nor quantitative insulin sensitivity check index can predict insulin resistance in elderly patients with poorly controlled type 2 diabetes mellitus. *J Clin Endocrinol Metab* 87:5332–5335
46. **Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagishi T, Shoji T, Okuno Y, Morii H** 1999 Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulphonylureas. *Diabetes Care* 22:818–822
47. **Quon MJ** 2001 Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab* 86:4615–4617
48. **Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M** 2000 Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63