Differential Effects of Metformin and Troglitazone on Cardiovascular Risk Factors in Patients With Type 2 Diabetes

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OBJECTIVE — Traditional cardiovascular risk factors (CVRF) only partly explain the excessive risk of cardiovascular disease in patients with type 2 diabetes. There is now an increasing appreciation for many novel CVRF that occur largely as a result of insulin resistance and hyperinsulinemia. Therefore, we investigated whether diabetes medications that vary in their mechanism of action and ability to reduce insulin resistance may differ in their effects on both traditional and novel CVRF.

RESEARCH DESIGN AND METHODS — We compared the addition of metformin or troglitazone therapy on CVRF in 22 subjects with type 2 diabetes who remained in poor glycemic control (with HbA_{1c} >8.5%) while taking glyburide 10 mg twice daily. Subjects were initially randomized to either metformin 850 mg once daily or troglitazone 200 mg once daily. Both medications were then titrated upward as needed to achieve fasting plasma glucose <120 mg/dl. Measures of glucose control, insulin resistance, and CVRF (blood pressure, lipids, plasminogen activator inhibitor-1, C-reactive protein, fibrinogen, and small dense LDL) were assessed both before and after therapy.

RESULTS — After 4 months of treatment, both metformin and troglitazone led to similar decreases in fasting plasma glucose and HbA_{1c}. The reduction in insulin resistance determined by hyperinsulinemic-euglycemic clamp was nearly twofold greater with troglitazone than metformin. Metformin did not induce significant changes in blood pressure, LDL cholesterol, LDL size, HDL cholesterol, triglycerides, or plasminogen activator inhibitor-1. However, C-reactive protein did decrease by 33% (6 ± 1 to 4 ± 1 ng/l; $P < 0.01$). Troglitazone therapy was associated with increases in LDL size (26.21 ± 0.22 to 26.56 ± 0.25 nm; $P = 0.04$) and HDL cholesterol (33 ± 3 to 36 ± 3 mg/dl; $P = 0.05$) and decreases in triglycerides (197 ± 19 to 155 ± 23 mg/dl; $P = 0.07$) and C-reactive protein by 60% (8 ± 3 to 3 ± 1 ng/l, $P < 0.01$).

CONCLUSIONS — For patients with type 2 diabetes in whom maximal sulfonylurea therapy failed, the addition of the insulin sensitizer troglitazone seemed to have greater benefits on several traditional and novel CVRF than metformin therapy. These differences were not related to glycemic improvement but reflected, in part, the greater reduction in insulin resistance obtained with addition of troglitazone. These data suggest that medications that more effectively address this underlying metabolic defect may be more beneficial in reducing cardiovascular risk in type 2 diabetes.

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Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; GDR, glucose disposal rate; Lp(a), lipoprotein (a); PAI-1, plasminogen activator inhibitor 1; PPAR-γ, peroxisome proliferator–activated receptor-γ; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

A predominant complication of type 2 diabetes is accelerated development of atherosclerosis. Despite the completion of several large intervention studies, it remains unclear whether glucose lowering, a fundamental component of diabetes therapy, is an effective method to reduce the incidence or progression of macrovascular disease in patients with type 2 diabetes (1,2). Moreover, other traditional cardiovascular risk factors (CVRF; i.e., those recognized and treated by most practicing physicians) only partly explain the excess risk of developing atherosclerosis in type 2 diabetes (3,4). This result is not surprising, because it has become increasingly evident that atherogenesis is a very complex event with multiple etiologies and processes that operate separately or in concert to elicit cardiovascular disease (CVD). Lipoprotein infiltration and retention in the arterial intima, activation of cells within the artery wall, endothelial cell dysfunction, oxidative stress, local and systemic inflammation, abnormal coagulation, and fibrinolysis may all be important contributors to the development of atherosclerosis (5,6). As a consequence of this broader understanding of the multitude of mechanisms responsible for atherosclerosis, there is increasing appreciation for the many less widely recognized or novel CVRF that contribute to these events or at least reflect the activity of these processes.

It has been recognized for some time that type 2 diabetes is associated with an increased prevalence of several traditional risk factors, including hypertension, elevated plasma triglycerides, and low HDL cholesterol levels (7). It has been demonstrated that these risk factors may result, in part, because of the underlying insulin resistance and hyperinsulinemia commonly present in type 2 diabetes (3,7,8). It is now apparent that many novel CVRF, including plasminogen activator inhibitor 1 (PAI-1), C-reactive protein (CRP), fibrinogen, and small dense LDL, may also be part of the insulin resistance syndrome (9–13). Given the apparent strong relationship between insulin resistance and

many traditional and novel CVRF, it would seem logical that more uniform reductions in these risk factors and perhaps a greater inhibition of atherosclerosis may be obtained by glucose-lowering agents that also substantially improve insulin resistance. Of relevance to this concept, a recent study (14) showed that troglitazone, a relatively potent insulin sensitizer, successfully reduced carotid arterial wall thickness in patients with type 2 diabetes. Furthermore, several studies have demonstrated that the thiazolidinedione class of medications can have favorable effects on coagulation/fibrinolysis factors, LDL particle size, and markers of inflammation (15,16). Metformin, which may also have modest insulin-sensitizing action, has also been demonstrated to have beneficial effects on several less traditional CVRF in some but not all studies. Moreover, when used as monotherapy in obese subjects in the U.K. Prospective Diabetes Study (UKPDS), metformin was associated with a significant decrease in CVD. However, in additional subanalyses of this same study, the combination of metformin and a sulfonylurea agent was associated with increased CVD (17).

This latter finding may have important implications, because current recommendations for management of hyperglycemia in patients with diabetes favor a goal-directed stepped-care approach; therefore, most hyperglycemic individuals will be placed relatively rapidly on multiple diabetes medications. It is becoming increasingly important, therefore, to consider the effect of combinations of diabetes medications on levels of traditional and novel CVRF.

Therefore, we compared the effects of two antidiabetic medications, metformin and troglitazone, which differ in their primary mechanisms of action on both traditional and novel CVRF in subjects already taking a maximal dose of sulfonylurea. To ensure that differences in levels of CVRF resulting from these therapies were not a consequence of dissimilar glycemic control, the study was specifically designed to achieve equivalent levels of plasma glucose in both treatment groups. This study demonstrates that in type 2 diabetic patients in whom maximal sulfonylurea therapy has failed, the addition of the insulin sensitizer troglitazone seemed to have greater benefits on several traditional and novel CVRF than metformin therapy.

RESEARCH DESIGN AND METHODS

— A total of 33 subjects (30 men, 3 women) with poorly controlled type 2 diabetes were enrolled in this study. Study entrance criteria included fasting plasma glucose >140 mg/dl and HbA_{1c} >8.5% while taking a half-maximal or greater dose of a sulfonylurea agent. No patients had clinical evidence of acute diabetic complications or other major medical illnesses. During the initial run-in phase of the study, in all patients, existing oral hypoglycemic therapy was switched to glyburide 10 mg twice daily for at least 1 month. At the end of this initial treatment phase, 22 patients (20 men, 2 women) still met the hyperglycemic inclusion criteria noted above. These subjects were allowed to continue in the study and were admitted into the research unit for baseline studies, which included 24-h blood pressure monitoring, anthropometric measurements, in vivo measures of insulin resistance, and fasting blood tests for plasma glucose, insulin, lipids, high-sensitivity CRP, PAI-1, fibrinogen, lipoprotein (a) [Lp(a)], and LDL size. After baseline studies were performed, subjects were randomized to receive additional treatment with either metformin 850 mg once daily or troglitazone 200 mg once daily. Patients were instructed to consume a weight-maintenance diet and to monitor capillary glucose values at least twice daily throughout the entire study. Patients taking antihypertensive or lipid-lowering medications were maintained on stable doses of these medications during the study. Patients were seen weekly for the first month and then biweekly for three additional months. If fasting plasma glucose levels were consistently >120 mg/dl after 2–4 weeks, the dose of troglitazone was titrated upward to a maximum of 600 mg/dl at 2- to 4-week intervals. Metformin was increased in a similar schedule to 850 mg twice daily and then 850 mg three times per day, as tolerated. If the fasting plasma glucose continued to be >180 mg/dl for 4–8 weeks on maximum doses of glyburide and either metformin or troglitazone, or if medication side effects developed, the patients were switched from metformin to troglitazone (or vice versa). These medications were also quickly titrated up to maximum dose based on the level of glycemic control, as described above. During the study, two patients who were originally started on troglitazone were switched to metformin and one patient taking metformin was switched to troglitazone. These three patients were given at least two additional months of therapy with these alternative agents before the treatment phase was completed. All but two patients in the metformin group and four patients in the troglitazone group were on maximum-dose therapy by the end of the study. At the end of this treatment phase, subjects were readmitted to the research unit to repeat the measurements performed at the baseline evaluation. All subjects provided informed consent before participation in the study. The study was conducted in the Special Diagnostic and Treatment Unit and General Clinical Research Center Scatter Beds in the Veterans Affairs Medical Center (San Diego, CA). The experimental protocol was approved by the Veterans Medical Research Foundation of San Diego and the Committee on Human Investigation at the University of California, San Diego.

Height and weight were measured by standard procedures and recorded in centimeters and kilograms, respectively. BMI was used to estimate the overall adiposity of the subjects. Maximum waist circumference was measured at the level of the umbilicus. All measurements were recorded with the subjects in a standing position with the arms at rest at their sides and were performed by a single registered dietitian trained in anthropometry.

Using ambulatory blood pressure monitors (Spacelabs, Redmond, WA), 24-h blood pressures were measured and recorded. Patients were required to wear the ambulatory blood pressure monitors on the left arm for the full 24-h period. Readings were recorded every 30 min from 0600 to 1800 h and every 60 min from 1800 to 0600 h. Mean systolic and diastolic pressure values were calculated from the 24-h recorded values.

Fasting plasma glucose was measured using the glucose oxidase technique on an automated autoanalyzer (Yellow Springs Instruments, Yellow Springs, OH). Total glycosylated hemoglobin was determined by the Bio-Rad variant procedure (Hercules, CA).

Blood for the determination of serum insulin levels was collected in untreated tubes and allowed to clot at room temperature. Serum insulin levels were measured by a specific double-antibody radioimmunoassay according to the

Table 1—*Characteristics of study patients enrolled in metformin and troglitazone treatment groups*

	Metformin	Troglitazone
Age (years)	56 ± 2	56 ± 2
Sex (male/female)	11/1	9/1
Weight (kg)	96.3 ± 8.3	110.4 ± 5.4
BMI (kg/m^2)	31.6 ± 2.7	36.3 ± 2.2
Fasting plasma glucose (mg/dl)	224 ± 12	192 ± 10*
HbA_{1c} (%)	9.2 ± 0.4	8.6 ± 0.3
Fasting insulin (mU/l)	36.6 ± 5.7	40.6 ± 7.1
GDR (mg · kg^{-1} · min^{-1})	6.15 ± 0.49	5.21 ± 0.71

Data are means ± SEM or *n*. *Significant at $P = 0.05$.

method of Desbuquois and Aurbach (18) by the Core Lab, Clinical Research Center, University of California, San Diego. In vivo measures of insulin resistance were determined using a 3-h hyperinsulinemic (300 mU · m^{-2} · min^{-1}) euglycemic (90 mg/dl) clamp, as described in detail previously (19). Glucose disposal rate (GDR) in each patient was calculated during the last 30 min of each clamp study from the glucose infusion rate corrected for changes in glucose pool size.

Blood for total cholesterol, triglycerides, LDL, and HDL was collected in EDTA-treated tubes using standard techniques. Samples were kept frozen or refrigerated, depending on the stability of the particular analyte. All lipid and lipoprotein testing was performed in a commercial testing center (Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA). For these and all subsequent assays, each subject's pretreatment and posttreatment samples were tested in the same run. Plasma cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol were all measured using a Hitachi 917 automated chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using commercially available reagents. Plasma total cholesterol and triglycerides were measured using the high-performance cholesterol and triglyceride/GPO assays from Boehringer Mannheim (Indianapolis, IN) using the peroxidase/phenol-4-aminophenazone indicator reaction and a peroxide-based colorimetric assay of glycerol (after performing a complete hydrolysis of triglycerides), respectively. LDL cholesterol and HDL cholesterol were measured using the N-genous LDL cholesterol and N-genous HDL cholesterol assays (Genzyme Diagnostics, Cambridge, MA). Fibrinogen activity was measured by clot detection using the Dade Thrombin Reagent (Dade Behring, Newark, DE). Lp(a) was determined by an immunoprecipitin, turbidometric method, DiaSorin SPQ II Lp(a) assay, using a Bayer automated chemistry analyzer (Bayer Diagnostics, Norwood, MA). CRP was determined using a commercially available latex-enhanced, high-sensitivity, fixed-time nephelometric assay (Dade Behring). PAI-1 antigen was measured in platelet-depleted plasma by enzyme-linked immunosorbent assay (Diagnostica Stago, Asnieres-Sur-Seine, France). LDL subparticle size was determined using nondenaturing gradient gel electrophoresis based on the method of Krauss and Burke (20).

Means and SEM were calculated for outcome variables both pretreatment and posttreatment with metformin or troglitazone. For each treatment, the percentage of change from pretreatment values was tested to determine whether it differed significantly from zero using a paired Student's *t* test if normal assumptions were valid or a nonparametric Wilcoxon's signed-rank test otherwise. When comparing treatments, the outcome variable was compared in terms of percentage of change between pretreatment and posttreatment using independent Student's *t* tests or nonparametric Wilcoxon's rank-sum tests.

RESULTS

Baseline characteristics

Subjects in both treatment groups were similar in age (56 ± 2 years; Table 1). Subjects randomized to the metformin group started the study with slightly higher fasting plasma glucose (224 ± 12 vs. 192 ± 10 mg/dl, $P < 0.05$) and HbA_{1c} (9.2 ± 0.4 vs. 8.6 ± 0.3%, $P = 0.32$). In contrast, the troglitazone group tended to be heavier (110.4 ± 5.4 vs. 96.3 ± 8.3 kg, $P = 0.19$) and had a greater BMI on average (36.3 ± 2.2 vs. 31.6 ± 2.7 kg/m^2, $P = 0.20$) than the metformin group (Table 1).

Changes in glycemic control and insulin levels

Both metformin and troglitazone treatment caused significant decreases in fasting plasma glucose (32 and 36%, respectively; $P < 0.001$ for both groups) compared with baseline levels. HbA_{1c} decreased by 17% in the metformin group and by 19% in the troglitazone group, a significant and similar decrease in both treatment arms ($P < 0.001$ for both groups; Table 2). Therefore, the addition of each of these agents to maximal glyburide therapy led to similar decreases in levels of glucose control by the end of the

Table 2—*Percentage of change in glycemic control, fasting plasma insulin, and GDR with metformin and troglitazone treatment*

	Metformin		Troglitazone		
	Percentage of change	*P*	Percentage of change	*P*	Metformin vs. Troglitazone (*P*)
Fasting plasma glucose (mg/dl)	−32	0.001	−36	<0.001	0.90
HbA_{1c} (%)	−17	≤0.001	−19	≤0.001	0.72
Insulin levels (mU/l)	−6	0.31	−18	0.08	0.30
GDR (mg · kg^{-1} · min^{-1})	21	0.048	55	0.004	0.14

Table 3—*Fasting plasma lipid levels before and after treatment with metformin or troglitazone*

	Metformin (n = 12)			Troglitazone (n = 10)			
	Before	After	P	Before	After	P	Metformin vs. Troglitazone (P)
Total cholesterol (mg/dl)	155 ± 10	145 ± 9	0.31	170 ± 10	167 ± 8	0.94	0.52
Triglycerides* (mg/dl)	199 ± 30	179 ± 29	0.13	197 ± 19	155 ± 23	0.07	0.33
LDL cholesterol (mg/dl)	70 ± 6	71 ± 6	0.57	90 ± 5	89 ± 4	0.82	0.87
HDL cholesterol (mg/dl)	31 ± 2	29 ± 2	0.14	33 ± 3	36 ± 3	<0.05	0.01

Data are means ± SEM. Statistical comparisons are based on percentage of change. *One outlier was excluded from metformin group because of marked hypertriglyceridemia (>800 mg/dl).

study. Fasting insulin levels decreased (but not significantly) in both groups as a result of treatment (6% in the metformin group, 18% in the troglitazone group). GDR increased significantly in both groups (21 ± 9% in the metformin group, $P = 0.048$; 55 ± 21% in the troglitazone group; $P = 0.004$). Of note, although the difference did not reach statistical significance, the increase in GDR in the troglitazone group was more than twofold that in the metformin group.

Anthropometric measurements

After 4 months of troglitazone therapy, mean body weight increased from 110.4 ± 5.4 to 114.8 ± 5.8 kg ($P < 0.01$) and BMI increased from 36.3 ± 2.2 to 37.7 ± 2.3 kg/m^2 ($P = 0.01$). In the subjects treated with troglitazone, abdominal circumference also increased by 5% (116.4 ± 5.4 to 121.9 ± 5.2 cm, $P < 0.001$). In the metformin group, there was no significant change in body weight, BMI, or abdominal circumference.

Blood pressure control

Mean 24-h systolic blood pressure was unchanged in the metformin group (130 ± 5 to 132 ± 4 mmHg, $P = 0.66$) but tended to be lower in the subjects treated with troglitazone by the end of the study (127 ± 4 to 123 ± 3 mmHg, $P = 0.36$). Similarly, diastolic blood pressure increased from 80 ± 3 to 81 ± 2 mmHg ($P = 0.70$) in the metformin group and decreased from 76 ± 3 to 70 ± 3 mmHg ($P = 0.12$) in the troglitazone group. None of these changes were statistically significant.

Lipid levels

Troglitazone therapy induced a 21% decrease in plasma triglyceride levels (197 ± 19 to 155 ± 23 mg/dl, $P = 0.07$) and an 11% increase in HDL levels (33 ± 3 to 36 ± 3 mg/dl, $P = 0.05$; Table 3). Metformin induced 10 and 6% decreases in triglyceride and HDL levels, respectively (neither change was statistically significant). Total and LDL cholesterol levels did not change significantly in either group.

Novel cardiovascular risk factors

Levels of PAI-1, fibrinogen, and CRP decreased in both the troglitazone and metformin groups after therapy (Table 4). However, only the decrease in CRP was statistically significant in both treatment groups. Of note, the decrease in CRP induced by troglitazone was significantly greater than that caused by metformin (60 vs. 33%, $P \leq 0.04$ between treatment groups), although the absolute level obtained in both groups was similar. As shown in Table 4, Lp(a) levels increased significantly only in the subjects treated with troglitazone (33 ± 13 to 47 ± 18 mg/dl, $P < 0.01$). LDL particle size increased from 26.21 ± 0.22 to 26.56 ± 0.25 nm in the troglitazone group ($P = 0.04$) and was unchanged in the metformin group (Fig. 1).

As noted above, previous reports have indicated that insulin resistance is related to several traditional and nontraditional CVRF. Therefore, we performed correlation analysis between GDR and selected CVRF. With pretreatment and posttreatment values from all subjects combined, GDR was positively correlated with HDL ($r = 0.34$, $P < 0.05$) and Lp(a) levels ($r = 0.27$, $P = 0.09$) and inversely related to CRP levels ($r = -0.41$, $P < 0.01$). Increases in GDR in both treatment groups combined were significantly associated with increases in LDL size ($r = 0.43$, $P = 0.05$), HDL levels ($r = 0.35$, $P < 0.05$), and levels of Lp(a) ($r = 0.44$, $P < 0.05$).

CONCLUSIONS — There were several major aims of this study. The first was to determine whether diabetes agents with different mechanisms of action would have different effects on levels of traditional and novel CVRF, independent of differences in glucose control. Second, we also wished to determine whether the addition of metformin therapy in individuals already taking a sulfonylurea agent may negatively affect novel CVRF in a fashion that may explain the adverse outcome associated with this combination

Table 4—*Novel cardiovascular risk factors before and after treatment with metformin or troglitazone*

	Metformin (n = 12)			Troglitazone (n = 10)			
	Before	After	P	Before	After	P	Metformin vs. Troglitazone (P)
Fibrinogen (mg/dl)	295 ± 22	270 ± 19	0.46	309 ± 21	287 ± 21	0.46	0.97
CRP (mg/l)	6 ± 1	4 ± 1	<0.01	8 ± 3	3 ± 1	<0.01	0.04
PAI-1 (ng/ml)	74 ± 24	64 ± 17	0.68	93 ± 26	72 ± 25	0.19	0.15
Lp (a)* (mg/dl)	22 ± 7	24 ± 8	0.84	33 ± 13	47 ± 18	<0.01	<0.01

Data are means ± SEM. Statistical comparisons are based on percentage of change. *One outlier was excluded from the metformin group for lipemic sample.

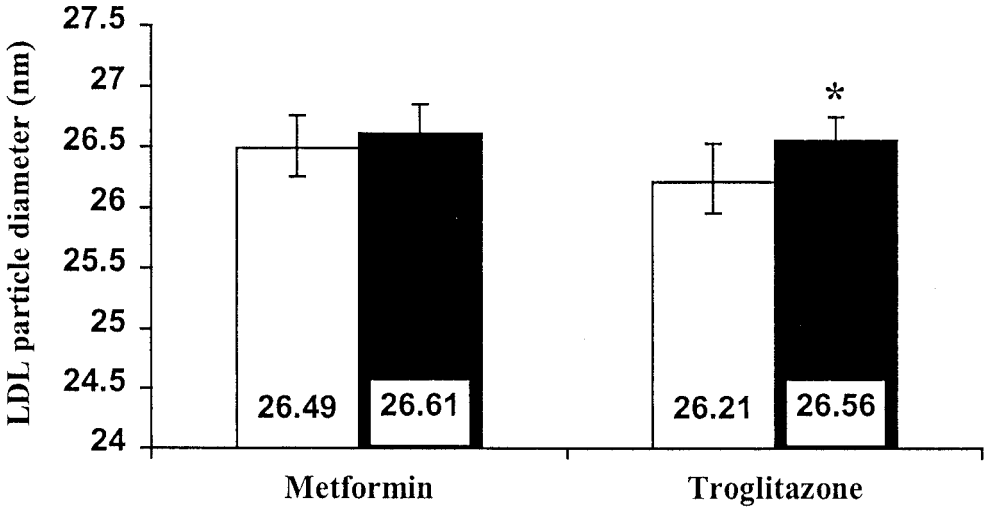

Figure 1— *Diameter of LDL particles before and after treatment with metformin or troglitazone. Data are means ± SEM. *P < 0.05.*

therapy in the UKPDS (17). Finally, because both metformin and troglitazone have been reported to improve the extent of underlying insulin resistance, we also wished to determine whether this metabolic feature was related to levels of CVRF.

To appropriately address these questions, it was essential that the two different therapies induce similar levels of glucose control. Therefore, we designed our study with this goal in mind. Both treatments decreased fasting blood glucose and HbA_{1c} levels to a similar extent and to levels that were not significantly different by the end of the study. Despite similar improvements in glucose control, troglitazone demonstrated a trend toward greater reductions in insulin levels, suggesting greater improvements in insulin resistance. This was mirrored by a similar trend toward greater increases in insulin-stimulated glucose disposal in subjects treated with troglitazone. In fact, troglitazone seemed to be more than twice as effective as metformin (Table 2) in enhancing insulin-mediated glucose disposal, a result that is consistent with prior comparison studies (21,22) and with the potent insulin-sensitizing activity of troglitazone (23).

Although metformin has been shown to cause a modest decrease in blood pressure in several studies (24), most studies have failed to demonstrate that metformin alters blood pressure levels (25–27). Our study indicates that addition of metformin therapy in subjects taking sulfonylurea did not reduce blood pressure. Although changes in blood pressure in the subjects treated with troglitazone were not statistically significant, there was a trend toward lower day-long systolic and diastolic blood pressures. Previous studies have reported that troglitazone therapy has significantly reduced diastolic blood pressure (28,29), whereas decreases in systolic blood pressure have been less consistent (29,30).

Metformin therapy seemed to induce a modest (10%, not significant) decrease in triglyceride levels while having no effect on LDL levels. These changes are consistent with previously reported effects of metformin on lipid levels. Metformin has been shown to reduce triglycerides by 10–30% (25,26,31), whereas reductions in total cholesterol and LDL cholesterol have been more modest (5–10%) (25,31,32). Although HDL actually decreased slightly in this study, plasma HDL is usually either unchanged or slightly increased by metformin in most studies (26). Changes in lipid levels were more favorable in the troglitazone group: triglyceride levels decreased by 21% and HDL increased by 9%. These findings are in agreement with previous studies showing that troglitazone characteristically lowered triglyceride levels by 15–20% (21,22,33,34) and increased HDL cholesterol levels by 5–8% (21,29,35). Consistent with the reduction in triglyceride levels, LDL size also increased on troglitazone therapy. This too has been a consistent finding in previous studies of troglitazone therapy (16,21,36). In contrast to several previously published studies (21,36,37), no increase in LDL cholesterol levels was noted in the troglitazone group.

Metformin therapy also had favorable but modest effects on several nontraditional CVRF. Fibrinogen and CRP both decreased, although only the decrease in CRP achieved statistical significance. This is consistent with previous reports that metformin may decrease levels of fibrinogen (38). A rather novel result was the impressive decrease in CRP that occurred with metformin therapy, a finding that deserves additional investigation. Moreover, these findings indicate that instituting metformin therapy in subjects already taking an oral sulfonylurea agent does not adversely affect the traditional or novel CVRF assessed in this study. Therefore, if this combination regimen predisposes to increased mortality, as suggested by several recent studies (17,39), it does not seem to be operating through a worsening of CVRF. However, it is possible that there may be other CVRF not measured in this study that are negatively altered by this combination of medications.

In addition to its increase in size of small dense LDL, troglitazone seemed to have beneficial effects on several other novel CVRF. Decreases in fibrinogen, PAI-1, and CRP levels were approximately 7, 22, and 66%, respectively, in the troglitazone group. This impressive decrease in CRP was significantly greater than the decrease in CRP that occurred in the metformin group. Although decreases in PAI-1 levels in individuals receiving troglitazone (15,40) have been reported

previously, there has been less evaluation of this agent's effects on fibrinogen and CRP (15,41).

In contrast to the many beneficial effects of troglitazone therapy on CVRF described above, it was also found to significantly increase Lp(a) levels. This effect has also been reported in other small studies (42,43), suggesting that this may not be a chance finding. Of note, Lp(a) levels correlated relatively well with glucose disposal, suggesting that insulin resistance or insulin levels may contribute to regulation of this lipoprotein. The significance of elevated Lp(a) levels in this setting will need to be determined in larger long-term studies.

The design of this study does not allow us to determine to what extent improvements in CVRF observed with both therapies are related to unique attributes of these medications or simply a function of their glucose-lowering effects. Because glucose levels improved to the same degree in both treatment groups, these studies suggest that the differential effects on CVRF detected between metformin and troglitazone are not related to differences in glucose control. Although it is possible that the small (and not statistically significant) differences in glucose control at the end of therapy could have contributed to differences in risk factor modification, a more likely explanation is that metformin and troglitazone have different effects on insulin resistance in type 2 diabetes. Although metformin increased the insulin-mediated glucose disposal rate by >20%, this is similar to the improvements obtained with sulfonylurea agents or insulin in subjects that were initially in poor control (44,45). This degree of improvement in insulin resistance is presumably related, in part, to reduced glucose toxicity. In another study that directly compared metformin and troglitazone therapy, insulin-mediated glucose disposal was also significantly greater in subjects treated with troglitazone (23). As noted earlier, many CVRF seem to be modulated by proinsulin, insulin, or insulin resistance (7,46) and are frequently elevated in insulin-resistant conditions (6,7,47). In agreement with this concept, levels of several novel CVRF correlated with measures of insulin resistance in this study. Agents that substantially improve insulin resistance, such as troglitazone, may therefore prove more useful in reducing levels of these risk factors.

Alternatively, troglitazone may have additional benefits on CVRF as a result of its unique mechanism of action. Troglitazone is a peroxisome proliferator–activated receptor-γ (PPAR-γ) ligand that has many direct effects on gene regulation (22,48,49), which may influence levels of CVRF. In addition, PPAR-γ ligands have potent anti-inflammatory effects, including inhibition of macrophage activation and secretion of cytokines, smooth muscle proliferation, and endothelial cell expression of adhesion molecules (50,51). These nonhypoglycemic effects of troglitazone (37) may reduce local and systemic inflammation and contribute to reductions in levels of acute-phase proteins, such as fibrinogen, CRP, and markers of vascular injury such as PAI-1.

An important limitation of this study was the relatively small number of subjects in both treatment groups. The unexpected withdrawal of troglitazone by the Food and Drug Administration led to a premature halt to the current study, thus limiting the analysis of data in the 22 subjects who were qualified to receive metformin or troglitazone therapy and had already completed the study. It is quite possible that if the decreases in blood pressure, levels of triglycerides, PAI-1, and fibrinogen observed in the first 10 subjects to take troglitazone had persisted in the subsequent subjects, these differences may also have achieved statistical significance. Although troglitazone is no longer available in the U.S., several other agents from this class of medications are now approved by the Food and Drug Administration for use in patients with type 2 diabetes. These medications not only are potent insulin sensitizers but, like troglitazone, may also have favorable effects on a variety of CVRF (52,53).

Strategies to prevent the increased development of CVD by aggressive glycemic control with conventional diabetes medications have had limited success. This may be related, in part, to the failure of these agents to also improve the myriad of CVRF associated with type 2 diabetes. The current studies suggest that both metformin and troglitazone may have beneficial effects on cardiovascular risk beyond their reduction in glucose levels. Moreover, in this relatively small study, troglitazone seemed to have greater effects on several traditional and novel CVRF than did metformin. Of interest, these more favorable changes in risk factors occurred in the troglitazone group despite significant increases in weight and BMI. This finding is of importance because many of these CVRF are positively associated with fat mass and may be regulated, in part, by adipocyte-related cytokines (54). These data suggest that mechanisms of weight gain in subjects treated with troglitazone are not invariably associated with elevations in cardiovascular risk factors. This may result from the propensity of troglitazone to induce weight gain via fluid retention and/or accumulation of subcutaneous fat rather than increases in visceral adipose tissue (37,55). Alternatively, the beneficial effects of enhanced insulin sensitivity or PPAR-γ activation may override the detrimental consequences of increased adipose accumulation on levels of CVRF.

One can speculate that these differences between diabetes agents may have important implications for progression of atherosclerosis and development of clinical events, because each of these risk factors has been associated with either an increased prevalence or a greater future risk of CVD. For example, as demonstrated in the UKPDS, moderate improvements in just one risk factor such as blood pressure may dramatically reduce CVD in patients with type 2 diabetes (56). These studies provide further support for the concept that diabetes medications may vary in their ability to reduce risk of CVD. However, long-term studies will be needed to determine whether greater improvements in these CVRF will translate into reduced CVD.

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