Metabolic Effects of Troglitazone Therapy in Type 2 Diabetic, Obese, and Lean Normal Subjects

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OBJECTIVE — To characterize metabolic effects of troglitazone in type 2 diabetic, obese, and lean subjects, and examine the effects of troglitazone 2–3 weeks after discontinuation.

RESEARCH DESIGN AND METHODS — Nine type 2 diabetic, nine obese, and nine lean subjects underwent baseline metabolic studies including an 8-h meal-tolerance test (MTT) and a 5-h glucose clamp. Subjects then received troglitazone (600 mg/day) for 12 weeks and subsequently had repeat metabolic studies. Diabetic subjects remained off hypoglycemic agents for 2–3 weeks and then underwent a 5-h glucose clamp.

RESULTS — In diabetic subjects, fasting plasma glucose was reduced ($P < 0.05$) and insulin-stimulated glucose disposal (R_d) was enhanced by treatment ($P < 0.02$). The area under the MTT 8-h plasma glucose curve declined with therapy ($P < 0.001$), and its change was positively correlated with the improvement in R_d ($r = 0.75$, $P < 0.05$). There was also a positive correlation between the change in fasting hepatic glucose output (HGO) and the change in fasting plasma glucose with treatment ($r = 0.92$, $P < 0.001$). Discontinuation of therapy for 2–3 weeks did not significantly affect fasting plasma glucose or insulin-stimulated glucose R_d. In obese subjects, insulin-stimulated glucose R_d improved with therapy ($P < 0.001$), allowing for maintenance of euglycemia by lower plasma insulin concentrations ($P < 0.05$). In lean subjects, an increase in fasting HGO ($P < 0.001$) and glucose clearance ($P < 0.01$) was observed.

CONCLUSIONS — Troglitazone lowers fasting and postprandial plasma glucose in type 2 diabetes by affecting both fasting HGO and peripheral insulin sensitivity. Its effects are evident 2–3 weeks after discontinuation. In obese subjects, its insulin sensitizing effects suggest a role for its use in the primary prevention of type 2 diabetes.

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Troglitazone has been shown to improve glycemic control in type 2 diabetes by augmenting peripheral insulin sensitivity (1–4). Its effects on hepatic glucose output (HGO) are less clear (1,5). Troglitazone also improves peripheral insulin sensitivity in obese insulin-resistant individuals, allowing for maintenance of normoglycemia by lower plasma insulin concentrations (6). This, along with the finding that troglitazone may improve β-cell function in subjects with impaired glucose tolerance (7), suggests that it may have a role in the primary prevention of type 2 diabetes.

In the present study, we further characterized the metabolic effects of troglitazone in subjects with type 2 diabetes and obesity. Lean subjects with normal glucose tolerance were also examined, because there are no existing data on the metabolic effects of prolonged troglitazone therapy in this population. In additon, we studied the metabolic effects of troglitazone 2–3 weeks after discontinuation in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects

Nine type 2 diabetic, nine obese (BMI >26 kg/m^2), and nine lean subjects (BMI <26 kg/m^2) were studied. Clinical characteristics are given in Table 1. All were in good general health and had normal renal and liver function. Diabetic subjects were on oral hypoglycemic agents (sulfonylurea and/or metformin), which were discontinued 2–3 weeks before baseline investigations. The experimental protocol was approved by the Committee on Human Investigation of the University of California, San Diego. Informed written consent was obtained from each subject.

Study design

Subjects were hospitalized for baseline metabolic studies, which consisted of an 8-h meal-tolerance test (MTT) on the first hospital day and a 5-h hyperinsulinemic (80 mU $\cdot$ m^{-2} $\cdot$ min^{-1}) euglycemic clamp with indirect calorimetry on the following day. After completion of baseline studies, subjects began troglitazone (600 mg/day). They were readmitted after 12 weeks of treatment for repeat metabolic studies identical to those at baseline. Diabetic subjects then remained off of hypoglycemic agents for 2–3 weeks and were then readmitted for a 5-h glucose clamp.

Meal-tolerance test

An 8-h MTT was performed after a 10-h overnight fast. A cannula was inserted into an antecubital vein for sampling. After two basal blood samples, subjects

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Abbreviations: $AUC_{C\text{-}Pep}$, area under the 8-h plasma C-peptide curve; AUC_{gluc}, area under the 8-h plasma glucose curve; AUC_{ins}, area under the insulin curve; CV, coefficient of variation; FFA, free fatty acid; HGO, hepatic glucose output; MTT, meal-tolerance test; NEFA, nonesterified fatty acid; PPAR-γ, peroxisome proliferator–activated receptor-γ; R_a, rate of glucose appearance; R_d, rate of glucose disappearance; RIA, radioimmunoassay; RQ, respiratory quotient.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline clinical characteristics of the study subjects*

Characteristic	Diabetic	Obese	Lean
Age (years)	49 ± 11	43 ± 8	47 ± 7
Sex (M/F)	7/2	7/2	8/1
Weight (kg)	100 ± 18	103 ± 11	74 ± 7
BMI (kg/m^2)	33 ± 5	35 ± 5	24 ± 2
Fasting glucose (mmol/l)	10.6 ± 0.9	5.1 ± 0.1	4.9 ± 0.1
Serum fructosamine (μmol/l)*	302 ± 19	205 ± 6	203 ± 27
HbA_{1c} (%)	7.9 ± 0.3	5.0 ± 0.1	5.0 ± 0.2

Data for age, weight, and BMI are means ± SD. Data for glucose, fructosamine, and HbA_{1c} are means ± SEM. Data for sex are *n*. *Normal laboratory range = 174–286 μmol/l.

were fed a liquid meal (10 kcal/kg; 50% carbohydrate, 34% fat, 16% protein) at 0800. Blood samples were taken at 30-min intervals during the first h and then every 60 min during the subsequent 3 h for measurement of plasma glucose, insulin, and C-peptide concentrations. A similar meal was consumed at 1200, followed by an identical blood sampling schedule.

Euglycemic clamp

Studies were performed in the morning after a 10-h overnight fast. At 0300, an 18-gauge cannula was inserted in an antecubital vein, and a constant infusion of [3-^{3}H]-glucose (0.35 μCi/min) (Du Pont-NEN, Boston, MA) was started. At 0700, a hand vein was cannulated in a retrograde fashion, and the hand was heated for sampling of arterialized blood. Beginning at 0800, four basal blood samples were obtained at 10-min intervals for measurement of plasma glucose concentration and specific activity, insulin, C-peptide, and nonesterified fatty acid (NEFA) concentrations. In diabetic subjects, the coefficient of variation (CV) for plasma-specific activity of these four samples ranged from 0.9 to 9.1% (mean = 3.1%) with no trend toward an increase in specific activity during the 30-min period. A hyperinsulinemic-euglycemic clamp (80 $mU \cdot m^{-2} \cdot min^{-1}$ for 5 h) was performed as previously described (8). Blood samples were taken for measurement of plasma glucose concentration every 5 min and for plasma-specific activity, insulin, C-peptide, and NEFA levels every 20–30 min. A variable infusion of [3-^{3}H]-glucose–enriched 20% glucose was delivered to maintain a plasma glucose concentration of 5 mmol/l. During the final 40 min of the insulin infusion, blood samples were obtained at 10-min intervals for determination of plasma glucose concentration and specific activity, insulin, C-peptide, and NEFA levels.

Whole-body glucose and lipid oxidation

Substrate oxidation rates in the basal state and during the glucose clamps were determined by indirect calorimetry, as previously described (9). Oxygen consumption and CO_2 production were measured for 15 min during the second half of each 30 min of the clamp, and the mean of the values during the last 10 min of the measurement interval was used for calculations. A timed basal urine sample (−5 h) and a postclamp urine sample were obtained for determination of basal and clamp urinary nitrogen (N) excretion rates. The nonprotein respiratory quotient (RQ) and carbohydrate and lipid oxidation rates were calculated using standard equations (9).

Analytical procedures

Plasma glucose was measured by a glucose oxidase method using a Yellow Springs analyzer (YSI 2700; Yellow Springs, OH). For determination of [^{3}H]-glucose–specific activity, 0.65 ml of plasma were deproteinized with $Ba(OH)_2/ZnSO_4$ and processed as previously described (9). Aliquots of the labeled glucose infusate were added to nonradioactive plasma and processed in parallel with the plasma samples to allow calculation of the [3-^{3}H]-glucose infusion rate.

Serum insulin was measured by a double antibody technique (10). The intra- and interassay CVs were 3.7 and 9.2%, respectively. C-peptide was measured by radioimmunoassay (RIA) (11) with an intra- and interassay CV of 6 and 10%, respectively. Serum triglyceride was measured using a GPO-PAP kit (Boehringer Mannheim, Mannheim, Germany) with an intra- and interassay CV of 1.4 and 1.7%, respectively. Serum free fatty acid (FFA) was determined using an acyl-CoA oxidase-based colorimetric kit (WAKO NEFA-C, Richmond, VA) with intra- and interassay CVs of 2.4 and 3.3%, respectively. Urinary nitrogen excretion was calculated from the urine concentrations of creatinine, uric acid, and urea (9).

Calculations

The rates of total glucose appearance (R_a) and disappearance (R_d) were calculated from the [3-^{3}H]-glucose data using the nonsteady-state equations of Steele (12). A distribution volume of 0.19 l/kg and a pool fraction of 0.5 were used in the calculations (13). HGO was calculated as the difference between total glucose R_a and the rate of exogenous glucose infusion. Fasting glucose clearance was calculated as the ratio of fasting glucose disposal to the fasting plasma glucose concentration.

Statistical analysis

Results are expressed as means ± SE unless otherwise indicated. The areas under the curves for each parameter were calculated using the trapezoidal rule. Statistical differences between treatments were sought using paired Student's *t* test. Correlations were sought by Pearson's least-squares method. A P value of <0.05 was considered statistically significant.

RESULTS — No significant change in body weight occurred after 12 weeks of troglitazone treatment in any group.

Glycemic control

In diabetic subjects, fasting plasma glucose was significantly reduced after 12 weeks of therapy (10.6 ± 0.9 vs. 8.1 ± 0.6 mmol/l, $P < 0.05$). It remained lower than baseline and no different than the 12-week value, 2–3 weeks after discontinuation of troglitazone (9.0 ± 0.6 mmol/l). Plasma fructosamine and HbA_{1c} levels were unchanged after 12 weeks of treatment (fructosamine, 302 ± 19 vs. 275 ± 16 μmol/l; HbA_{1c}, 7.9 ± 0.3 vs. 7.4 ± 0.4%) and tended to be lower than baseline 2–3 weeks after discontinuation of therapy (fructosamine, 273 ± 151 μmol/l; HbA_{1c}, 7.1 ± 0.4%).

Three of the nine diabetic subjects were considered nonresponders to troglitazone. We arbitrarily defined nonresponders as subjects whose fasting plasma glucose concentrations fell by <10% and

Table 2—*Fasting plasma C-peptide, insulin, and lipid concentrations at baseline and with 12 weeks of troglitazone therapy*

	Diabetic		Obese		Lean	
	Baseline	12 weeks	Baseline	12 weeks	Baseline	12 weeks
C-peptide (nmol/l)	0.95 ± 0.10	0.79 ± 0.12*	0.81 ± 0.07	0.64 ± 0.06*	0.47 ± 0.06	0.46 ± 0.06
Insulin (mU/l)	20.5 ± 4.5	15.4 ± 3.3	11.9 ± 2.3	9.0 ± 1.6†	3.7 ± 0.7	5.3 ± 1.6
NEFA (mmol/l)	0.55 ± 0.07	0.42 ± 0.07	0.36 ± 0.08	0.21 ± 0.05	0.24 ± 0.05	0.28 ± 0.04
Cholesterol (mg/dl)						
Total	181 ± 12	171 ± 12	169 ± 10	185 ± 14	182 ± 12	195 ± 13
HDL	35.4 ± 1.1	37.2 ± 0.8	33.4 ± 2.0	36.0 ± 2.6†	43.4 ± 2.7	44.2 ± 3.2
LDL	109 ± 8	101 ± 6	102 ± 8	119 ± 9	119 ± 11	128 ± 12
Triglyceride (mg/dl)	178 ± 33	161 ± 36	168 ± 27	146 ± 30‡	98 ± 7	114 ± 15

Data are means ± SEM. *$P < 0.02$, †$P < 0.05$, and ‡$P = 0.06$ compared with baseline.

whose HbA_{1c} was reduced by an absolute value of <0.5% after 12 weeks of treatment. The six diabetic subjects who responded to troglitazone showed a significant reduction in fasting plasma glucose (10.9 ± 1.2 vs. 7.3 ± 0.5 mmol/l, $P < 0.05$), as well as serum fructosamine (320 ± 24 vs. 275 ± 20 µmol/l, $P < 0.01$) with therapy. Fasting plasma glucose remained unchanged after troglitazone was discontinued for 2–3 weeks (8.5 ± 0.6 mmol/l). In the obese and lean groups, fasting plasma glucose, fructosamine, and HbA_{1c} were not affected by therapy.

Fasting plasma insulin, C-peptide, and lipid concentrations

In diabetic subjects, a reduction in fasting plasma C-peptide concentration and a trend toward lower fasting insulin levels occurred after 12 weeks of troglitazone (Table 2).

In obese subjects, both fasting plasma C-peptide and insulin concentrations were reduced by 12 weeks of therapy. Fasting plasma C-peptide and insulin concentrations did not change after troglitazone in lean subjects.

Baseline fasting NEFA concentrations were significantly higher in the diabetic group compared with the obese and lean subjects. Fasting NEFA levels were not altered by therapy in any of the groups.

Meal-tolerance tests

The plasma glucose, C-peptide, and insulin response curves during the MTT for diabetic and obese subjects are shown in Fig. 1. After 12 weeks of troglitazone, the area under the 8-h plasma glucose curve (AUC_{gluc}) was reduced in the diabetic subjects (121 ± 8 vs. 84 ± 7 mmol · l^{-1} · h, $P < 0.001$). In these subjects, there was a positive correlation between the decrease in AUC_{gluc} and the improvement in insulin sensitivity with therapy ($r = 0.75$, $P < 0.05$). Postprandial plasma glucose levels were unchanged in the obese and lean groups.

In the diabetic subjects, the area under the 8-h plasma C-peptide curve ($AUC_{C\text{-}Pep}$) during the MTT was reduced by 20% with treatment (20 ± 2 vs. 16 ± 2 nmol · l^{-1} · h, $P < 0.05$). The area under the insulin curve (AUC_{ins}) tended to decrease with therapy.

In the obese subjects, the $AUC_{C\text{-}Pep}$ was reduced by 20% with therapy (20 ± 2 vs. 16 ± 1 nmol · l^{-1} · h, $P < 0.005$). As in the diabetic group, AUC_{ins} tended to be lower with treatment.

In the lean group, there was no change in $AUC_{C\text{-}Pep}$ or AUC_{ins} with troglitazone.

Insulin-stimulated glucose disposal

Mean plasma insulin levels during the final 40 min of the glucose clamp ranged from 115 to 142 mU/l in the three groups and were not significantly different between studies. In the diabetic subjects, insulin-stimulated glucose R_d during the final 40 min of the glucose clamps increased by 36% after treatment (4.4 ± 0.6 vs. 6.0 ± 0.8 mg · kg^{-1} · min^{-1}, $P < 0.02$) and remained significantly higher than baseline and no different from the 12-week treatment value, 2–3 weeks after discontinuation of troglitazone (5.5 ± 0.7 8 mg · kg^{-1} · min^{-1}, $P < 0.01$ compared with baseline) (Fig. 2). Insulin-stimulated glucose R_d was also significantly increased by troglitazone in the obese subjects (6.42 ± 0.45 vs. 8.31 ± 0.66 mg · kg^{-1} · min^{-1}, $P < 0.001$). No change in insulin sensitivity was observed after therapy in the lean subjects (Fig. 2).

Substrate oxidation

Basal carbohydrate and lipid oxidation rates were unchanged by drug treatment in all groups (data not shown). Nonoxidative glucose R_d was lower in the diabetic and obese subjects compared with lean control subjects and was significantly increased after troglitazone (Fig. 2). It remained improved in the diabetic subjects 2–3 weeks after cessation of therapy. Drug treatment had no effect on carbohydrate or lipid oxidation rates in any of the study groups.

Hepatic glucose output

Fasting HGO was lower after troglitazone in each diabetic subject considered a responder to therapy. In this subgroup, fasting HGO fell by 21% (2.35 ± 0.32 vs. 1.86 ± 0.12 mg · kg^{-1} · min^{-1}, $P < 0.05$ by Wilcoxon's signed-rank test) to levels similar to those of normal subjects. By contrast, fasting HGO remained unchanged in each of the three diabetic subjects considered nonresponders to troglitazone. There was a significant positive correlation between fasting HGO and fasting plasma glucose concentration in diabetic subjects at baseline and after 12 weeks of troglitazone (baseline, $r = 0.91$, $P < 0.001$; 12 weeks, $r = 0.87$, $P < 0.01$). There was also a positive correlation between the change in fasting HGO and the change in fasting plasma glucose after 12 weeks of troglitazone ($r = 0.92$, $P < 0.001$).

An increase in fasting HGO (1.84 ± 0.08 vs. 1.98 ± 0.06 mg · kg^{-1} · min^{-1}, $P < 0.001$) and fasting glucose clearance (0.38 ± 0.02 vs. 0.41 ± 0.01, $P = 0.006$) was observed after troglitazone in the lean group.

Fasting HGO did not change in the obese subjects treated with troglitazone (1.56 ± 0.05 vs. 1.56 ± 0.05 mg · kg^{-1} · min^{-1}). In this group, as in the diabetic and lean subjects, HGO was largely suppressed during the final 40 min of the glucose clamps and was unaffected by drug treatment.

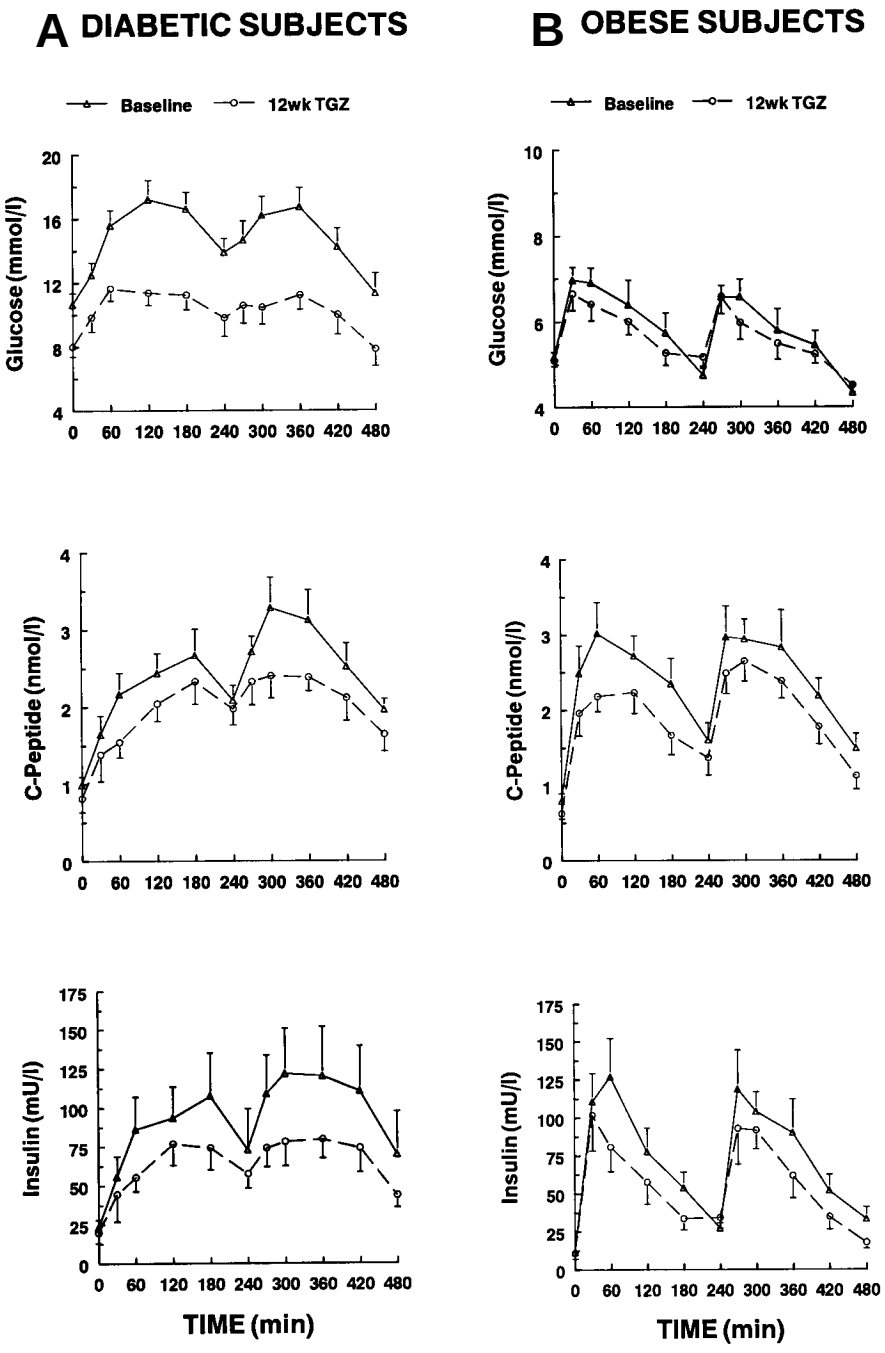

Figure 1—*Plasma glucose, C-peptide, and insulin response curves during the 8-h meal-tolerance test in diabetic (*A*) and obese (*B*) subjects.*

CONCLUSIONS — Insulin resistance is arguably the primary metabolic abnormality in type 2 diabetes (14). In the natural history of this disorder, normoglycemia is initially maintained in the face of peripheral insulin resistance by compensatory hyperinsulinemia. Eventually, if β-cell function deteriorates, glucose-induced insulin secretion declines, resulting in overt type 2 diabetes (15,16).

Troglitazone, a thiazolidinedione, has been demonstrated to lower plasma glucose and insulin levels in patients with type 2 diabetes primarily by improving peripheral insulin sensitivity (1,2). Its effects on HGO are less clear, with clinical trials arriving at differing conclusions (1,2,4). Troglitazone has also been shown to improve peripheral insulin sensitivity in obese subjects with both normal and impaired glucose tolerance, allowing for maintenance of normoglycemia by lower plasma insulin concentrations (6,17). To our knowledge, the length of time that troglitazone's effects on glycemic control and peripheral insulin sensitivity persist in diabetic subjects after its discontinuation has not previously been evaluated.

As anticipated, a significant reduction in fasting plasma glucose occurred after 12 weeks of troglitazone in diabetic subjects. This 24% decline in fasting plasma glucose was consistent with that previously observed using 400–600 mg troglitazone daily (3). When clinical nonresponders to therapy were excluded from analysis, fasting plasma glucose was reduced by 33%, and plasma fructosamine was also significantly lower than baseline after 12 weeks of therapy.

As in earlier studies, troglitazone did not affect glycemic control in a subpopulation of our diabetic subjects (nonresponders) (1,18). Characterization of metabolic traits that might predict response to troglitazone would be extremely important for clinical practice. It has previously been suggested that in spite of a positive effect on peripheral insulin sensitivity, troglitazone therapy will not improve parameters of glycemic control unless sufficient circulating levels of plasma insulin are present (16). Though the number of patients we studied was too small to adequately evaluate this hypothesis, two of the three clinical nonresponders did have the lowest plasma insulin levels of the group (data not shown), reaffirming that adequate plasma insulin concentrations may be one metabolic characteristic predicting response to therapy.

It appears that the changes in fasting glycemia produced by therapy were the result of changes in basal HGO. The effect of troglitazone on HGO is less clear than its effect on peripheral insulin sensitivity. Results from previous studies have been conflicting (1,3,4), with the discrepancy possibly related to the dose of troglitazone studied. Maggs et al. (3) recently reported a relative suppression of basal HGO after 12 weeks of 600 mg troglitazone per day. No change in basal HGO was observed at lower doses (3). Inzucchi et al. (4) found no effect on HGO after 12 weeks of treatment with 400 mg troglitazone per day. It is generally accepted that elevated basal HGO is the primary cause of fasting hyperglycemia in patients with type 2 diabetes and that in this population, there is

a correlation between fasting HGO and fasting plasma glucose (19). We found a strong positive correlation between fasting plasma glucose and basal HGO both before and after 12 weeks of troglitazone. HGO decreased with therapy in each of the diabetic subjects showing a favorable glycemic response to therapy (responders). By contrast, in the three nonresponders, HGO did not change after 12 weeks of therapy. This, along with the positive correlation observed between the change in basal HGO and the change in fasting plasma glucose occurring with therapy, suggests that 600 mg/day of troglitazone does affect basal HGO, and that this, at least in part, is the mechanism by which it lowers fasting plasma glucose.

Postprandial glycemia and insulin-stimulated glucose disposal during the clamp studies both improved after troglitazone treatment in the diabetic subjects. The decrease in postprandial glucose levels was positively correlated with the improvement in peripheral insulin sensitivity. In addition, there was a significant reduction in fasting and postprandial plasma C-peptide levels, implying a decrease in insulin secretion. These data are in keeping with previous studies indicating that troglitazone improves glycemic control primarily via its peripheral insulin sensitizing effects.

In the obese subjects, as has been shown previously (6), our principal finding was the improvement in peripheral insulin sensitivity with therapy, which allowed for maintenance of euglycemia by significantly lower plasma insulin concentrations. Though not directly examined in this study, troglitazone therapy has been shown to positively affect both β-cell secretory function and glucose sensing ability in subjects with impaired glucose tolerance (5) and to improve β-cell function in type 2 diabetic subjects, as suggested by a lowered plasma proinsulin/immunoreactive insulin ratio (20). Though the mechanism by which this effect occurs remains to be elucidated, these findings are important and clinically relevant because they suggest a role for insulin sensitizers in the primary prevention of type 2 diabetes and in preserving β-cell function in established type 2 diabetes.

In both the diabetic and obese subjects, the improvement in insulin-stimulated glucose disposal was not accompanied by a change in the rate of carbohydrate oxidation. It follows, therefore, that nonoxidative glucose metabolism was enhanced. Shulman et al. (21) have previously shown that glycogen synthesis accounts for the great majority of nonoxidative glucose metabolism in both normal and diabetic subjects under hyperinulinemic-hyperglycemic conditions. Impairment of glycogen synthase activity is known to be a major metabolic defect in type 2 diabetes (22). Recently, Park et al. (23) have reported that in muscle cultures of type 2 diabetic and obese subjects, chronic (4 days) troglitazone exposure increases both insulin-independent and insulin-dependent glucose uptake and glycogen synthase activity. Our indirect calorimetry data are consistent with these in vitro studies.

In nondiabetic lean subjects, we found that troglitazone produced an increase in fasting glucose clearance, which was accompanied by an augmentation in basal HGO, thereby resulting in no change in fasting plasma glucose. Though we did not examine the cellular mechanisms responsible for this effect, previous in vitro experiments have shown troglitazone-induced increases in GLUT1 mRNA and protein in 3T3-L1 adipocytes, suggesting this as a mechanism by which troglitazone may augment insulin-independent glucose disposal in vivo (24). It has been proposed that troglitazone acts by binding to peroxisome proliferator-activated receptor-γ (PPAR-γ), leading to changes in transcription rates of PPAR-γ responsive genes (25–27). Insulin-stimulated glucose R_d was not affected by therapy in lean subjects. This finding, along with the fact that therapy in insulin-resistant diabetic and obese subjects resulted in a significant increase in peripheral insulin sensitivity, suggests that the gene or gene product affected by troglitazone and responsible for the increase in insulin sensitivity is deficient either quantitatively or qualitatively in insulin-resistant subjects, but normal in lean subjects with normal insulin sensitivity.

Two weeks after the cessation of therapy in the diabetic subjects, measures of glycemic control as well as insulin-stimulated glucose disposal remained significantly improved compared with baseline values and unchanged from values at 12 weeks of therapy. This extended action after discontinuation is in keeping with troglitazone's effects on gene transcription and protein synthesis. If, in fact, this finding is unique to troglitazone's mechanism of action, its sustained antidiabetic effect would have important clinical implications including possible changes in dosing schedule. Because short-term interruptions of treatment would not necessarily alter glycemic control, transient discontinuation of therapy (i.e., for intercurrent illness or surgery), without the need for intervening treatment, would be possible. The duration of clinical effects after discontinuation of troglitazone is also important in relation to clinical trials studying antidiabetic medications. Our findings indicate that patients treated with troglitazone who are entering

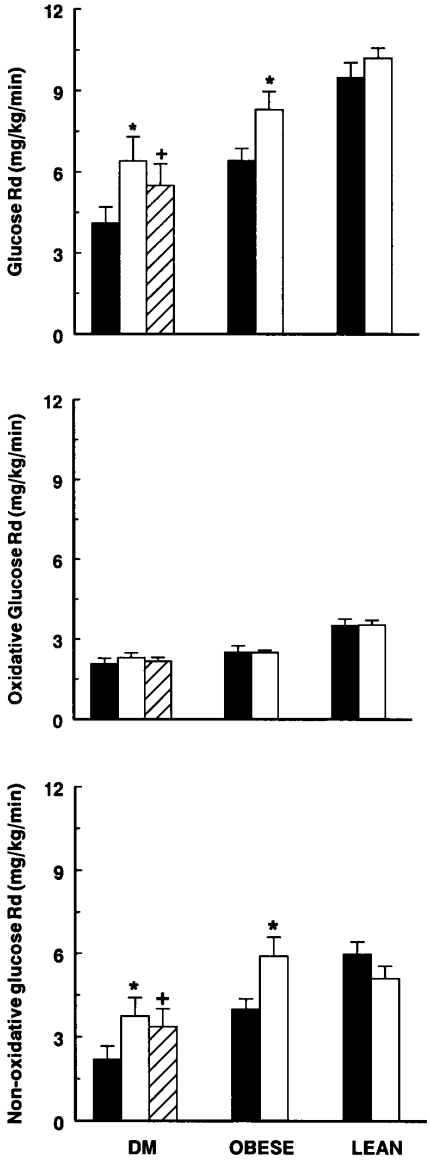

Figure 2—*Insulin-stimulated total, oxidative, and nonoxidative glucose disposal (R_d) at baseline (■), 12 weeks troglitazone treatment (□), and 2–3 weeks after troglitazone treatment (▨) in diabetic (DM), obese, and lean subjects.* *P < *0.02 compared with baseline, +No change compared with 12 weeks treatment.*

clinical trials requiring discontinuation of medication must undergo a washout period of >3 weeks to ensure adequate baseline measurements.

In summary, troglitazone improved fasting and postprandial glycemic control in diabetic subjects by affecting both fasting HGO and peripheral insulin sensitivity. In obese subjects, it improved insulin sensitivity, allowing for a significant reduction in plasma insulin concentrations while maintaining normoglycemia. Fasting glucose clearance and HGO were increased in lean subjects, although insulin-stimulated glucose metabolism remained unchanged. The beneficial effects of troglitazone therapy on insulin sensitivity and glycemic control in diabetic subjects were long-lived and evident 2–3 weeks after its discontinuation.

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