Further Insight on the Hypoglycemic and Nonhypoglycemic Effects of Troglitazone 400 or 600 mg/d: Effects on the Very-Low-Density and High-Density Lipoprotein Particle Distribution

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The effects of troglitazone 400 or 600 mg/d on the glycemic control, very-low-density lipoprotein (VLDL), and high-density lipoprotein (HDL) subclass concentrations and plasminogen-activator inhibitor 1 (PAI-1) levels were assessed in patients with type 2 diabetes that had not been controlled with dietary treatment. This was a multicenter, open-label, parallel-groups study. It included a run-in 4-week diet period and a 24-week randomized treatment. Fifty one patients received 400 mg/d and 55 patients 600 mg. The mean HbA_{1c} concentration at the end of the study was similar for both doses. Troglitazone, regardless of dose, significantly improved insulin sensitivity assessed by the homeostasis model (HOMA). PAI-1 levels were significantly decreased in both groups by 13%. Higher HDL cholesterol concentrations and lower triglycerides levels were observed at the end of treatment. Triglyceride contents were reduced only in the lighter VLDL1. The change in HDL cholesterol concentration resulted from a combination of increased HDL3 cholesterol and lower HDL2 cholesterol levels. No differences were found in the effects of both treatment groups on the evaluated parameters. Our data provide new information about the actions of the drug on the lipid profile. Troglitazone reduces triglyceride levels by lowering the triglycerides content of the VLDL1 particles and increases HDL cholesterol concentrations by increasing HDL3 cholesterol levels.

THE INTRODUCTION of troglitazone and other thiazolidinediones opened in the past few years a new oral alternative for diabetes therapy.[1-3] At the launching to the market, a putative mechanism of action was already known.[4]. Many groups considered these drugs as valuable tools for diabetes therapy,[5] as well as for studies of the pathophysiology of insulin resistance.[6].The drug has a different mechanism of action to the previously employed oral hypoglucemiants. Troglitazone specifically binds to a family of nuclear receptors, peroxisome proliferation activator receptors (PPAR γ-1). The drug acts as an activator or repressor of the expression of multiple genes involved in carbohydrate and/or lipid metabolism.[7-10] Multiple trials that have been completed or are underway demonstrate that the drug may also modulate the appearance of some of the diabetes-related complications, such as diabetic nephropathy or atherosclerosis.[10-15]

Numerous open or placebo-controlled studies have shown that troglitazone, used as monotherapy at doses from 200 to 800 mg/d, can improve indices of glucose control; reduction of fasting plasma glucose between 0.9 and 3.9 mmol/L and of HbA_{1c} between 0.4% and 2% have been reported.[16-25] A few trials compared the efficacy of the drug at various doses.[26-29] While some[26-28] described a dose-response relationship, others such as the European Multicenter Trial[29] found that doses of 200, 400, 600, and 800 mg were almost equipotent. Maggs et al[28] compared the effects of 200, 400, and 600 mg on the glycemic profile, insulin-stimulated glucose disposal rate, and hepatic glucose production measured during a hyperinsulinemic-euglycemic clamp. In the 400- and 600-mg/d groups, fasting glucose levels were decreased by a mean of 1.2 mmol/L and 2.5 mmol/L, respectively. Additional differences were observed among the groups. In the 600-mg group, levels of free fatty acids and hepatic glucose production were statistically significantly lower compared with the 400-mg group. In both groups, the insulin-stimulated glucose disposal rate increased by 45%. These data suggest that the effect of troglitazone on different metabolic pathways could be different depending on the dose used.

Previous studies have shown that thiazolidinediones can modify lipid metabolism in insulin-resistant animals and humans.[30-33] Troglitazone reduces plasma triglycerides concentrations, decreases the formation of the small, dense low-density lipoproteins (LDLs) and increases the high-density lipoprotein (HDL) cholesterol levels, but increases the LDL cholesterol concentrations. The mechanism responsible for the troglitazone-induced triglycerides reduction has been partially characterized. In animals, a decreased hepatic very-low-density lipoprotein (VLDL) cholesterol synthetic rate has been noted.[34] In humans, an increased lipoprotein lipase mass and activity has been reported.[35] It remains to be described the lipoprotein subclass predominantly related to the triglycerides reduction or the effect of several doses of the drug on lipoprotein metabolism. Also, no information exists about the HDL subclass responsible for the increased HDL cholesterol concentrations found during troglitazone treatment.

The objectives of this study were to assess the effect of 2 doses of troglitazone, 400 and 600 mg/d, on the glycemic control, lipid profile, VLDL subclass distribution, plasminogen-activator inhibitor (PAI-1), and fibrinogen concentrations

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in patients with type 2 diabetes that had not been controlled with dietary treatment. Our purpose was to extend the observations regarding the dose-response effects of troglitazone on the different metabolic processes related to the insulin-resistance syndrome. Although troglitazone has been retired from the market, these results give new information about the hypolipidemic actions of the thiazolidinediones.

MATERIALS AND METHODS

Patients

All patients were previously diagnosed with type 2 diabetes according to the criteria of the American Diabetes Association and were 18 years or older. Their body mass index had to be between 28 and 35 kg/m^2 after 4 weeks of an isocaloric diet prescribed and supervised by a registered dietitian. Also, HbA_{1c} concentrations had to be above 8.5% and fasting plasma glucose higher than 8.8 mmol/L at study entry. Patients should have received no prior therapy for type 2 diabetes other than diet and exercise. Candidates were excluded if they had type 1 diabetes mellitus, uncontrolled hypertension, severe renal dysfunction, nephrotic syndrome, active liver disease, or hepatic enzyme elevation (serum aspartate aminotransferase [AST] or alanine aminotransferase [ALT] $>$ 2.5 times the upper limit of normal); in addition, females of childbearing potential not using barrier, nonhormonal intrauterine devices, or surgical contraception, pregnant or lactating females, subjects with symptomatic angina pectoris or cardiac insufficiency, or the occurrence of a major vascular event within 3 months prior to screening or diagnosis of a serious or chronic disease were excluded. Concomitant use of antiobesity medication, bile acid sequestrants, cyclosporine, or any drug with potential effects on lipid metabolism were not allowed during the study or in the previous 3 months.

The ethics committee of each of the participating institutions approved the protocol and every patient provided witnessed, written informed consent prior to entering the study. An external agency monitored the quality and reproducibility of the procedures in each center.

Study Design

This was a multicenter, open-label, parallel-groups study. It included a run-in 4-week diet period and a 24-week randomized treatment with troglitazone. Patients attended an initial screening visit followed by a qualifying visit 2 weeks later in which a registered dietitian assessed compliance with diet. Within 2 weeks patients returned for a baseline visit; blood samples were collected and drug treatment was allocated if the HbA_{1c} and fasting plasma glucose met the inclusion criteria. Patients who qualified were randomized to one of the troglitazone treatments: 400 mg or 600 mg. Patients were instructed to take 2 tablets daily for the 400-mg group and 3 tablets for the 600-mg group. The study medication was taken with breakfast. All patients were scheduled to come back 2 weeks later and then every 4 weeks until week 24 (visits 4 to 9). Throughout the trial, patients were required to comply with an isocaloric diet composed by 50% carbohydrates, 10% protein, 30% fat, and 30 g/d fiber. Dietary advice was given at the initial visit and compliance with the diet was assessed at every subsequent visit using a 3-day food record. Drug compliance was also measured at every visit.

Efficacy Parameters

The primary efficacy evaluation was based on the percent change in HbA_{1c} levels from baseline to week 24 (or at the end of active treatment). The baseline value was obtained after the 4-week lead-in diet period. Secondary efficacy evaluations were based on the percent change from baseline to week 24 for C-peptide, total insulin, proinsulin, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL subclass distribution, PAI-I, and fibrinogen concentrations. Insulin sensitivity was estimated using the homeostasis model (HOMA) score based on the formula: fasting serum insulin (μU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5, as described by Matthews et al.[36] With this method, high HOMA scores denote low insulin sensitivity

Safety Evaluation

Before entering the baseline phase, a complete physical examination and clinical laboratory evaluation were performed. The laboratory evaluation included a blood count, pregnancy test, urine examination, creatine kinase (CK) levels, liver function tests, and a glycemic profile (fasting plasma glucose, HbA_{1c}, and fructosamine). These tests were repeated at the end of the study. At each visit, the liver function tests and glycemic profile were measured. Patients were excluded from the study if they developed severe hyperglycemia or any other significant deviation from safety tests. An ALT or AST concentration 3 times above the upper limit of normal at 2 consecutive measurements 1 week apart ($\pm$3 days) was considered as indication for elimination from the study. Other reasons for dismissal were lack of compliance to the drug or diet.

Laboratory Analyses

The laboratory of the Department of Endocrinology and Metabolism of the Instituto Nacional de la Nutrición performed all lipid and clinical laboratory measurements using standardized procedures. This laboratory is certified for standardization of the tests by the External Comparative Evaluation of Laboratories Program of the College of American Pathologist. Blood samples were taken after an overnight fast (9 to 12 hours). All laboratory analysis was performed with commercially available standardized methods. Glucose was measured using the glucose oxidase method, and HbA_{1c} using latex immunoagglutination inhibition (Bayer Diagnostics, Tarrytown, NY).[37] Total serum cholesterol and triglycerides were measured using an enzymatic method (SERA-PAK, Bayer Diagnostics) (coefficient of variation [CV] 3.3%). HDL cholesterol was precipitated with fosfotungstic acid and Mg^{2+} (CV 2.5%). LDL cholesterol concentration was estimated by the Friedewald formula.[38] Direct LDL cholesterol was determined by ultracentrifugation (β quantification) at baseline and at the end of the treatment and in every patient in whom triglycerides levels were above 4.5 mmol/L.[39] Apoprotein B concentration was measured by an immunonephelometric method. Fructosamine concentration was measured using a reduction test with nitroblue tetrazolium (Bohringer Mannheim, Germany). PAI-1 antigen concentration was measured using an enzyme-linked immunosorbent assay (ELISA). Fibrinogen concentration was measuring using a commercially available kit based on the Claus method. Intact proinsulin and insulin concentrations were estimated using an ELISA method. Serum free fatty acids were measured using a colorimetric method (NEFA kit, Wako, Richmond, VA). C-peptide levels were measured by a radioimmunoassay procedure. VLDL subclass isolation was done using a density gradient ultracentrifugation method using a Beckman (Fullerton, CA) SW40 Ti rotor.[40] The cholesterol concentrations of the HDL subfractions were measured using a double precipitation assay.

Statistical Analysis

Statistical analysis was performed using the SAS Statistical Package version 6.12 TS020 (SAS Insitute, Cary, NC). Differences between groups were evaluated using the 2-tailed paired *t* test.

The intention-to-treat approach was used (n = 106). The mean percentage change in HbA_{1c} was tested by means of the paired *t* test). Triglycerides and lipoprotein(a) concentrations were compared after log transformation, due to skewed distribution of these variables. The baseline comparability of these 3 centers and the dose groups were

Table 1. Characteristics of the Patients Included in the Study

Variable	Total (n = 106)	400-mg Dose (n = 51)	600-mg Dose (n = 55)
Sex			
Male	40 (39.70%)	17 (33.3)	23 (41.8)
Female	66 (62.30%)	34 (66.7)	32 (58.2)
Age (yr)	51.23 ± 10.3	52.27 ± 10.1	50.27 ± 10.6
Weight (kg)	74.57 ± 11.82	73.94 ± 12.99	75.16 ± 10.79
Body mass index	29.79 ± 3.46	29.81 ± 3.79	29.78 ± 3.15
Diabetes duration (mo)	23.96 ± 38.74	22.62 ± 37.56	25.19 ± 40.08
Glucose (mmol/L)	9.5 ± 1.08	9.65 ± 1.06	9.46 ± 1.09
HbA_{1c} (%)	9.94 ± 1.8	9.81 ± 1.7	10.06 ± 2.01

estimated by ANOVA. The statistical significance of the differences between treatment groups was assessed using regression analysis. All tests were 2-sided and conducted at a 5% level of significance.

RESULTS

Patients

A total of 4,235 patients were included in the screening phase, from which 107 were selected for the study; 106 patients met the inclusion criteria and 1 patient was excluded during the diet phase. The characteristics and baseline measurements of the patients who entered the study are listed in Table 1. The characteristics of the patients were very homogeneous and there were no differences in the patients' baseline demographic parameters among sites or treatments. Fifty-one patients received 400 mg/d and 55 patients 600 mg/d of troglitazone. Adherence to treatment was greater than 80% for all patients, excepting those who dropped out before the end of the study. Nineteen patients did not complete the study. The reasons for exclusion were as follows: adverse events (n = 9), severe hyperglycemia (n = 2), and administrative difficulties (n = 8). The dropouts were homogeneously distributed along the study. Forty-one and 46 patients of the 400- and 600-mg groups, respectively, completed all of the efficacy evaluations.

Efficacy

As shown in Tables 2 and 3, troglitazone resulted in significantly lower levels of HbA_{1c} in both groups. The mean glucose and HbA_{1c} concentrations attained at the end of the study were similar for both doses. A HbA_{1c} level below 7% was achieved in the same proportion of patients in both groups at the end of the trial (32% and 30%, respectively). Both doses decreased fructosamine concentrations (18% and 14% for the 400- and 600-mg groups; $P > .05$). No significant changes in body weight were observed in any group. Diet adherence remained constant during the study in every case.

Effects on the Insulin Sensitivity and Insulin Secretion

Troglitazone, regardless of dose, significantly improved insulin sensitivity (Tables 2 and 3). HOMA scores were reduced to a mean of 38% and 44% in the 400- and 600-mg groups ($P > .05$ between groups). As expected, the reduction in insulin resistance resulted in lower insulin secretion rates, estimated by decreased concentrations of insulin, C-peptide, and proinsulin. In both groups, a remarkable reduction of the proinsulin concentrations (mean, 72% and 77%, respectively) was observed. This modification was significantly larger than the percentage reductions observed in the fasting insulin levels (11.4% and 33%, respectively). Percentage changes in C-peptide concentrations were of a similar magnitude (18.8% and 21%, respectively).

Effects on PAI-1 and Fibrinogen Concentrations

As shown in Tables 2 and 3, PAI-1 levels were significantly decreased in both groups by 13%. No significant changes were observed in fibrinogen concentrations.

Effects on Lipoproteins and Free Fatty Acids

No statistically significant changes were observed in the plasma concentration of cholesterol and LDL cholesterol in the groups or within the entire population. In accordance with these results, apolipoprotein B concentrations remained unmodified. As shown in Table 4, troglitazone significantly reduced fasting triglycerides concentrations in the population as a whole (2.38 ± 1.5 *v* 2.06 ± 1.3 mmol/L, $P = .03$); the same tendency was observed in both groups (particularly in the 600-mg arm), but no statistical significance was achieved (Tables 5 and 6). In the whole group, HDL cholesterol concentrations were higher at the end of treatment compared with baseline (0.99 ± 0.2 *v* 1.04 ± 0.2 mmol/L, $P = .01$); the same tendency was observed in only the 600-mg group, but no statistical significance was achieved. A clear trend for increased lipoprotein(a) concentrations was observed in both groups; statistical significance was

Table 2. Effects of Troglitazone 400 mg/d on Glycemic Profile, PAI-1, and Fibrinogen Concentrations

Variable	n	Basal (mean ± SD)	Post-treatment (mean ± SD)	*P*	Within-Patient Change (%)
Body mass index (kg/m^2)	51	29.81 ± 3.79	31.09 ± 4.87	.225	4.10 ± 0.5
HbA_{1c} (%)	51	9.81 ± 1.69	7.88 ± 1.92	.000	−19.60 ± 8.4
Glucose (mmol/L)	51	9.65 ± 1.07	7.49 ± 2.42	.000	−22.40 ± 6.8
C-peptide (nmol/L)	51	0.85 ± 0.53	0.69 ± 0.57	.024	−18.80 ± 13.60
Proinsulin (pmol/L)	51	4.15 ± 4.19	1.13 ± 2.05	.000	−72.70 ± 22.8
Insulin (pmol/L)	51	91.92 ± 62.04	81.36 ± 86.40	.021	−11.50 ± 16.0
Fructosamine (mmol/L)	51	334.63 ± 72.56	293.19 ± 94.42	.014	−12.40 ± 7.48
Fibrinogen (mg/dL)	51	300.52 ± 81.04	294.73 ± 54.23	.857	−2.00 ± 10.5
PAI-1 (mg/dL)	51	97.26 ± 47.04	84.63 ± 42.57	.024	−12.90 ± 24.0
HOMA score	51	6.17 ± 4.20	3.82 ± 4.10	.010	−38.00 ± 19.8

Table 3. Effects of Troglitazone 600 mg/d on Glycemic Profile, PAI-1, and Fibrinogen Concentrations

Variable	n	Basal (mean ± SD)	Post-treatment (mean ± SD)	*P*	Within-Patient Change (%)
Body mass index (kg/m^2)	55	29.78 ± 3.15	30.22 ± 5.79	.964	1.40 ± 0.3
HbA_{1c} (%)	55	10.06 ± 2.01	7.67 ± 1.13	.000	−23.80 ± 8.3
Glucose (mmol/L)	55	9.47 ± 1.10	6.88 ± 1.60	.000	−27.30 ± 6.5
C-peptide (nmol/L)	55	0.84 ± 0.47	0.66 ± 0.39	.145	−21.40 ± 24.9
Proinsulin (pmol/L)	55	4.58 ± 4.77	1.05 ± 1.90	.000	−77.00 ± 25.2
Insulin (pmol/L)	55	89.46 ± 56.70	59.58 ± 42.96	.085	−33.40 ± 26.7
Fructosamine (mmol/L)	55	334.67 ± 59.19	280.59 ± 64.71	.002	−16.10 ± 9.8
Fibrinogen (mg/dL)	55	296.97 ± 89.18	307.10 ± 65.86	.302	3.40 ± 11.80
PAI-1 (mg/dL)	55	86.86 ± 43.70	78.81 ± 39.25	.011	−9.20 ± 22.8
HOMA score	55	5.60 ± 3.20	2.50 ± 1.40	.001	−55.30 ± 14.7

attained after logarithmic transformation of lipoprotein(a) values.

Based on the fact that, in the majority of the studies, a lowering of triglycerides levels was reported, we wanted to identify the VLDL subclass related to this troglitazone action. VLDL triglycerides were significantly reduced ($P < .001$) in the whole population (Table 4). The triglycerides content of the lighter VLDLs (VLDL1) was reduced by 33.8% ($P = .001$). A smaller change (16.1%) was found in the triglycerides content of the VLDL2 particles. The opposite trend was found in the VLDL3 subclass; a statistically significant increase in triglycerides concentrations was observed (24.4%, $P = .01$). In accordance with the triglycerides changes, lower cholesterol and apoprotein B concentrations were also found in the VLDL1 and VLDL2 particles. However, these changes did not achieve statistical significance. An increased apoprotein B concentration was found in the denser VLDLs (VLDL3). No statistically significant differences were found between the effects of both treatments.

The cholesterol concentration of the HDL subclasses was measured to identify the particle responsible for the increased HDL cholesterol levels. As shown in Table 4, increased HDL cholesterol levels resulted from a highly significant increment of HDL3 cholesterol levels ($P = .003$). This change was counterbalanced by a small but statistically significant decrease in HDL2 cholesterol levels. No statistically significant differences were found between the effects of both treatments.

The free fatty acids concentration was lowered by the treatment. In both groups a reduction of 18% was observed at the end of treatment.

Safety

The safety analysis included all patients who entered the study. Nine patients were eliminated due to adverse events. Two cases were clearly related to the drug. One patient had increased concentrations of transaminases (3 times the upper normal level) after 8 weeks of treatment (600 mg). The transaminases concentrations returned to normal after 2 weeks of stopping the drug. An additional patient presented general-

Table 4. Effects of Troglitazone (400 and 600 mg/d) on Lipid Profile, and VLDL and HDL Subclassess

Variable	Basal (mean ± SD)	Post-treatment (mean ± SD)	*P*	Within-Patient Change (%)
Cholesterol (mmol/L)	5.42 ± 1.06	5.35 ± 1.33	.537	−1.29 ± 10.0
Triglycerides (mmol/L)	2.38 ± 1.52	2.06 ± 1.34	.030	−13.40 ± 19.3
HDL cholesterol (mmol/L)	0.99 ± 0.21	1.04 ± 0.21	.010	6.60 ± 15.8
LDL cholesterol (mmol/L)	3.31 ± 0.91	3.35 ± 0.94	.309	1.20 ± 16.60
Lipoprotein(a) (mg/dL)	11.50 ± 16.00	16.09 ± 20.00	.001	39.90 ± 30.00
Apoprotein B (g/L)	1.07 ± 0.30	1.04 ± 0.30	.510	−2.80 ± 18.00
HDL2 cholesterol (mmol/L)	0.21 ± 0.17	0.15 ± 0.12	.038	−28.50 ± 18.00
HDL3 cholesterol (mmol/L)	0.76 ± 0.21	0.85 ± 0.23	.003	11.80 ± 19.00
VLDL triglycerides (mmol/L)	1.85 ± 2.11	1.48 ± 1.31	.001	−20.00 ± 39.00
VLDL1 triglycerides (mmol/L)	1.22 ± 1.60	0.81 ± 0.72	.001	−34.40 ± 18.50
VLDL2 triglycerides (mmol/L)	0.50 ± 0.45	0.42 ± 0.39	.001	−16.00 ± 19.10
VLDL3 triglycerides (mmol/L)	0.22 ± 0.18	0.27 ± 0.23	.010	−22.70 ± 31.00
VLDL cholesterol (mmol/L)	1.36 ± 1.32	1.03 ± 0.82	.054	−24.20 ± 25.80
VLDL1 cholesterol (mmol/L)	0.64 ± 0.55	0.53 ± 0.42	.013	−17.10 ± 21.00
VLDL2 cholesterol (mmol/L)	0.32 ± 0.26	0.28 ± 0.23	.184	−12.50 ± 15.00
VLDL3 cholesterol (mmol/L)	0.22 ± 0.19	0.27 ± 0.24	.114	22.70 ± 25.00
VLDL1 apolipoprotein B (g/L)	0.051 ± 0.05	0.045 ± 0.038	.196	−11.70 ± 17.80
VLDL2 apolipoprotein B (g/L)	0.038 ± 0.03	0.035 ± 0.30	.312	−7.80 ± 11.50
VLDL3 apolipoprotein B (g/L)	0.034 ± 0.03	0.044 ± 0.37	.014	29.40 ± 16.20
Free fatty acids (mEq/L)	0.53 ± 0.22	0.43 ± 0.21	.001	−18.80 ± 8.70

Table 5. Effects of Troglitazone 400 mg/d on Lipid Profile, and VLDL and HDL Subclasses

Variable	Basal (mean ± SD)	Post-treatment (mean ± SD)	*P*	Within-Patient Change (%)
Cholesterol (mmol/L)	5.42 ± 1.04	5.27 ± 1.19	.447	−2.70 ± 11.9
Triglycerides (mmol/L)	2.19 ± 1.20	2.10 ± 1.28	.891	−4.10 ± 21.5
HDL cholesterol (mmol/L)	1.05 ± 0.25	1.03 ± 0.22	.810	−1.90 ± 13.9
LDL cholesterol (mmol/L)	3.32 ± 0.98	3.25 ± 0.50	.810	−2.10 ± 17.30
VLDL cholesterol (mmol/L)	1.28 ± 1.60	1.06 ± 0.79	.394	−17.10 ± 24.10
Lipoprotein(a) (mg/dL)	9.78 ± 9.60	13.41 ± 17.40	.026	37.00 ± 32.60
Apoprotein B (mg/dL)	109.95 ± 26.36	101.08 ± 25.22	.318	−8.09 ± 15.40
HDL2 cholesterol (mmol/L)	0.20 ± 0.17	0.13 ± 0.02	.05	−35.00 ± 17.60
HDL3 cholesterol (mmol/L)	0.82 ± 0.20	0.87 ± 0.22	.53	6.10 ± 16.80
VLDL triglycerides (mmol/L)	1.71 ± 1.59	1.72 ± 1.49	.66	0.50 ± 15.20
VLDL1 triglycerides (mmol/L)	1.01 ± 0.90	0.92 ± 0.83	.46	−8.90 ± 18.40
VLDL2 triglycerides (mmol/L)	0.53 ± 0.56	0.45 ± 0.37	.21	−15.10 ± 19.60
VLDL3 triglycerides (mmol/L)	0.23 ± 0.24	0.32 ± 0.42	.52	39.10 ± 26.40
Free fatty acids (mEq/L)	0.51 ± 0.26	0.41 ± 0.21	.04	−21.50 ± 11.50

ized edema of moderate intensity. Other reasons for stopping treatment were events probably not related to the drug. Episodes of duodenal ulcer, unstable angina, and acute pancreatitis were causes for the withdrawal of 3 patients. Three additional cases had dizziness and drowsiness, and the patients refused to continue the study. One patient dropped out of the study after 8 weeks of treatment due to the detection of asymptomatic liver cirrhosis. The only clinical abnormality detected during screening of this patient was a low normal platelet count; his liver function tests were normal in every evaluation and the diagnosis was based on ultrasonographic characteristics of the liver. The remaining patients did not show any significant increase of AST, ALT, or CK levels.

DISCUSSION

Our main objective was to extend the available information regarding the effects of troglitazone in several components of the insulin resistance syndrome and to compare the efficacy of 400 and 600 mg/d on these parameters. Our main findings are the description of VLDL and HDL subclasses responsible for the changes of the concentration of fasting triglycerides and HDL cholesterol concentrations. In March 2000, troglitazone was withdrawn because of reports of severe hepatic injury. However, rosiglitazone and pioglitazone became available in 1999 and are approved as monotherapy and in combination with other oral agents or insulin (pioglitazone). Close to 1,000,000 patients with type 2 diabetes are currently being treated with these drugs.[41] Since most of the hypoglycemic and nonhypoglycemic effects of the thiazolidinediones are shared between all the drugs of this group,[42] the results reported here may be still relevant for the understanding of the antiatherogenic actions of the thiazolidinediones.

In several clinical trials, troglitazone therapy significantly reduced triglycerides levels and increased HDL cholesterol.[21,24,28,30] Several reports indicate that troglitazone and pioglitazone decrease triglycerides levels.[43] The implications of this change in the atherogenicity of the lipid profile may vary depending on the type of triglyceride-rich particles modified by the treatment. Meanwhile, the plasma accumulation of the large VLDL subclasses (VLDL1) and the chylomicrons has not been related to an increased atherogenicity; the opposite had been considered for the increased concentration of the denser VLDL (VLDL3), intermediate-density lipoproteins, and chylomicron remnants.[44,45] In this report, troglitazone resulted in lower

Table 6. Effects of Troglitazone 600 mg/d on Lipid Profile, and VLDL and HDL Subclasses

Variable	Basal (mean ± SD)	Post-treatment (mean ± SD)	*P*	Within-Patient Change (%)
Cholesterol (mmol/L)	5.42 ± 1.08	5.42 ± 1.47	.970	0.00 ± 11.5
Triglycerides (mmol/L)	2.40 ± 1.78	2.03 ± 1.42	.139	−15.40 ± 22.9
HDL cholesterol (mmol/L)	0.97 ± 0.23	1.03 ± 0.25	.214	6.10 ± 15.4
LDL cholesterol (mmol/L)	3.30 ± 0.86	3.44 ± 0.94	.309	4.20 ± 21.00
VLDL cholesterol (mmol/L)	1.42 ± 1.29	1.03 ± 0.87	.034	−27.40 ± 24.20
Lipoprotein(a) (mg/dL)	13.18 ± 17.80	18.60 ± 23.00	.000	41.90 ± 39.10
Apoprotein B (mg/dL)	106.03 ± 33.11	108.09 ± 39.25	.614	1.80 ± 16.10
HDL2 cholesterol (mmol/L)	0.21 ± 0.18	0.18 ± 0.14	.654	−14.20 ± 19.10
HDL3 cholesterol (mmol/L)	0.75 ± 0.20	0.83 ± 0.23	.027	10.60 ± 15.90
VLDL triglycerides (mmol/L)	1.77 ± 1.74	1.44 ± 1.30	.219	−18.60 ± 16.30
VLDL1 triglycerides (mmol/L)	1.16 ± 1.42	0.76 ± 0.66	.076	−34.40 ± 25.70
VLDL2 triglycerides (mmol/L)	0.44 ± 0.32	0.42 ± 0.45	.272	−4.50 ± 9.40
VLDL3 triglycerides (mmol/L)	0.20 ± 0.13	0.26 ± 0.34	.381	30.00 ± 29.30
Free fatty acids (mEq/L)	0.54 ± 0.23	0.43 ± 0.21	.008	−20.30 ± 13.50

concentrations of fasting triglycerides and VLDL triglycerides. The triglycerides content of the lighter VLDL subclasses (VLDL1 and VLDL2) were significantly reduced by the treatment. In contrast, the number of VLDL3 particles was increased. These observations suggest that the primary mechanism of action for reducing triglycerides concentration is inhibition of triglycerides synthesis in the liver. These results are in accordance with animal studies recently reviewed by Sunayama et a.[46] PPAR-γ activation reduces free fatty acid release from adipose tissue and lowers plasma free fatty acid concentrations. As a result, hepatic VLDL production may decrease. Troglitazone reduces triglycerides concentrations even in mice lacking adipose tissue, suggesting that other complementary actions may contribute for the reduced hepatic triglycerides synthesis.[47] However, controversial results have been reported about the direct effects of thiazolidinediones on the hepatic lipogenesis and fatty acid oxidation.[47] This change may also result from an improved hepatic insulin action, based on the ability of insulin to suppress the secretion of the lighter, but not the denser, VLDL particles.[48] On the other hand, an increased conversion of the recently secreted VLDL1 and VLDL2 particles in VLDL3 particles may be explain the increased amount of VLDL3 particles, based on the fact that the VLDL3 particles mainly result from the conversion of the recently secreted VLDLs, rather than direct hepatic secretion.[49] This change must be mediated by an increased mass of the lipoprotein lipase caused by the PPAR-γ activation. The reduced plasma free fatty acid concentration may also increase the activity of this enzyme. In summary, we propose that the main action of troglitazone on VLDL metabolism is a decreased triglycerides secretion rate. The decreased triglycerides content in the VLDL particles may be one reason for the lower concentration of the smaller and denser LDL particles reported during troglitazone treatment.[31]

Several reports indicate that all the thiazolidinediones increase HDL. Since epidemiological studies suggest that the HDL2 particles are the only HDL particle related with decreased cardiovascular risk, it is important to identify the HDL subfraction responsible for the increased HDL cholesterol concentrations observed during troglitazone.[50] In this study, the change in HDL cholesterol was explained by increased concentrations of HDL3 cholesterol. A small but statistically significant lowering of the HDL2 cholesterol concentration was observed. The long-term consequences of this HDL modification remained to be described. Possible explanations for the increased HDL3 cholesterol concentration include the induction by troglitazone of the expression of ABCA1, a member of the adenosine triphosphate (ATP)-binding cassette transporter family, which is a main determinant for the concentration of the recently secreted HDL particles (ie, pre-β HDL or HDL3 particles) and the total HDL cholesterol levels.[51] Recent reports have proved that PPAR-γ activators induce expression of the gene encoding ABCA1.[52] These effects of thiazolidinediones might be mediated by their stimulatory action on LXR-α expression and activity. Repa et al demonstrated that the rexinoid-induced increased ABCA1 expression was associated to a significant increased HDL concentration.[53] The proposed mechanism may explain the increased HDL cholesterol not associated with any change in apolipoprotein a-I levels.[54] On the other hand, the decreased HDL2 cholesterol concentration could be explained by induction by troglitazone of the expression of the SRBI, a scavenger receptor that plays a major role in extracting cholesterol esters from HDL particles in the liver and other organs.[55] The large, apolipoprotein E–rich, HDL2 particles are the optimal substrates for this receptor.[56] If the postulated mechanisms are true, the resulting increased HDL3/decreased HDL2 concentrations may be a result of an efficient reverse cholesterol transport (and possibly an antiatherogenic action of the drug), in spite of the population-based, epidemiological evidence, which suggests that this change may not be protective against atherosclerosis. The proposed mechanism could be one of the explanations for the recently reported antiatherogenic effect of troglitazone.[57] Additional studies are required for describing the effects of thiazolidinediones on the HDL kinetics.

Increased lipoprotein(a) concentrations were observed in both groups. Ovalle and Bell described this abnormality previously.[58] We believe that the improvement of insulin sensitivity induced by the drug could explain the increased concentration of lipoprotein(a). The Insulin Resistance and Atherosclerosis Study (IRAS) group[59] has reported that insulin resistance is associated with lower concentrations of lipoprotein(a) regardless of apolioprotein(a) phenotype; however, the pathophysiology and clinical significance of this change remain to be described.

The data here reported confirm that troglitazone, 400 or 600 mg/d, is effective regardless of the dose reducing insulin resistance, HbA_{1c}, insulin secretion, and free fatty acids concentrations. HOMA scores, which provide an index of insulin sensitivity, were improved in 40%, confirming the well-known actions of the thiazolidinediones to reduce insulin resistance. The magnitude of the change in the HOMA scores is in accordance with the range of results reported in the European Multicenter Trial (34.3% to 42.8%). A significant reduction in insulin secretion was associated with the improvement in insulin sensitivity. In this report, insulin secretion was assessed using 3 parameters: fasting plasma insulin, intact proinsulin, and C-peptide concentrations. Proinsulin is considered as a marker of defective insulin secretion due to a premature release of immature granules. A disproportionate increase of plasma proinsulin levels have been reported in insulin-resistant subjects and newly diagnosed type 2 diabetic patients. Troglitazone therapy results in a remarkable reduction of proinsulin concentrations; the percentage change of this parameter was several times larger than the modifications observed in insulin or C-peptide concentrations. Our results are similar to those reported by Prigeon et al.[27] These investigators observed, in 18 cases treated with several doses of troglitazone, a larger reduction in proinsulin concentrations (42%) than in insulin levels (26%). These data suggest that troglitazone induces qualitative and quantitative changes in insulin secretion. These effects could not be explained solely by the elimination of toxic effects of glucose in insulin secretion because similar results have been published in normoglycemic insulin-resistant subjects.[60,61] Other possible explanations could be the elimination of toxic effects of free fatty acids,[62] direct effects of the drug on β cells,[3] or elimination of direct or indirect deleterious effects of insulin resistance on insulin secretion.[63]

Our data confirm that troglitazone has some beneficial hemorrheologic effects. PAI levels were significantly lowered by the treatment. Two previous groups reported that troglitazone treatment significantly decreased plasma levels of PAI-1 in patients with type 2 diabetes and those with polycystic ovary syndrome.[64,65] This effect is an indirect action of the drug, by diminishing the hyperinsulinemia accompanying amelioration of insulin resistance. Troglitazone also reduces the PAI-1 expression by the vascular wall cell elements; the opposite action is found in Hep G2 cells.[66] Our results differ from previous reports in the magnitude of the reduction in PAI-1 levels. In previous reports,[64,65] the change was close to 30%; here, PAI-1 levels decreased only by approximately 10%. The reasons for this difference include different measurement methods and the large variability in interindividual responses found in this and previous reports. As previously reported, no change in fibrinogen concentrations was observed.[65] These data suggest that the fibrinogen gene expression is not regulated by PPAR-γ receptors. Other insulin sensitizers, such as metformin, reduce fibrinogen concentrations. These data demonstrate the complex interaction between fibrinogen metabolism and insulin resistance.[67]

In conclusion, our data provide new information about the effects of this group of drugs on the lipid profile. Troglitazone reduces triglycerides levels by lowering the triglycerides content of the recently secreted VLDL particles and increases HDL cholesterol concentrations by increasing HDL3 cholesterol levels. The long-term consequences of these changes on the atherosclerotic process in humans remain to be described.

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