Effect of Peroxisome Proliferator–Activated Receptor γ Agonist Treatment on Subclinical Atherosclerosis in Patients With Insulin-Requiring Type 2 Diabetes

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OBJECTIVE — To determine the effect of thiazolidinedione treatment on subclinical atherosclerosis progression in insulin-requiring patients with clinical characteristics suggesting type 2 diabetes.

RESEARCH DESIGN AND METHODS — Eligible participants (n = 299) were randomized within strata of baseline common carotid artery (CCA) intima-media thickness (IMT) (<0.8 mm, ≥0.8 mm) to 400 mg troglitazone daily or placebo for 2 years. A general linear mixed-effects model was used to compare the rate of change in CCA-IMT between treatment groups.

RESULTS — Overall, average rates of CCA-IMT change were not significantly different between troglitazone- and placebo-treated subjects (0.0030 ± 0.021 vs. 0.0066 ± 0.021 mm/year; P = 0.17). In the stratum of subjects with CCA-IMT ≥0.8 mm, troglitazone significantly reduced the progression of CCA-IMT relative to placebo (0.0013 ± 0.022 vs. 0.0084 ± 0.023 mm/year; P = 0.03). Fasting glucose, insulin, and HbA_{1c} were significantly lower in troglitazone- versus placebo-treated subjects (P < 0.01). Whereas blood pressure significantly differed between treatment groups in the ≥0.8-mm stratum, there was no difference between treatment groups in the <0.8-mm stratum.

CONCLUSIONS — Insulin sensitization and reduction in blood pressure may be contributory mechanisms by which troglitazone reduced subclinical atherosclerosis progression in this cohort of well-controlled insulin-dependent patients with clinical characteristics suggesting type 2 diabetes.

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Type 2 diabetic patients have a 2- to 4-times-greater risk for cardiovascular events than people without diabetes (1). People with type 2 diabetes also have increased carotid arterial wall thickness, a marker of subclinical atherosclerosis (2). Although the mechanisms by which diabetes accelerates atherosclerosis and promotes clinical events are unclear, the etiology appears to be multifactorial and includes abnormalities of glucose, blood pressure, and lipoproteins (3).

Thiazolidinedione (TZD) drugs activate nuclear peroxisome proliferator–activated receptor (PPAR)γ. TZDs reduce insulin resistance and lower serum insulin levels in diabetic and nondiabetic individuals. They also lower exogenous insulin requirements in insulin-treated type 2 diabetic patients (4). TZDs also have beneficial effects on lipid levels (5), lower peripheral vascular resistance (6), and increase arterial compliance and lower blood pressure (7). TZDs also have direct arterial effects that limit proliferation of vascular endothelial and smooth muscle cells in vitro (8) and have reduced carotid artery intima-media thickness (IMT) in short-term studies (9,10). These findings suggest that TZDs may have antiatherogenic properties. The Troglitazone Atherosclerosis Regression Trial was conducted to determine whether management of insulin-treated patients with clinical characteristics suggesting type 2 diabetes with a TZD could reduce subclinical atherosclerosis progression.

RESEARCH DESIGN AND METHODS

— The Troglitazone Atherosclerosis Regression Trial was a single-center, randomized, double-blind, placebo-controlled trial conducted from 24 January 1997 to 20 May 2000. Eligible participants were aged 30–70 years, diagnosed with diabetes at age ≥30 years, had a fasting glucose <19.4 mmol/l (350 mg/dl), and were receiving ≤150 units of insulin daily without concomitant antidiabetes medications. Eligible participants entered an 8- to 12-week run-in phase, during which insulin doses (four injections per day at breakfast, lunch, dinner, and bedtime) were adjusted to achieve (self-monitored) fasting and 30-min premeal capillary whole-blood glucose concentrations 5.6–8.3 mmol/l (100–150 mg/dl). Trial eligibility criteria at the end of the run-in phase were attendance at ≥75% of scheduled visits, per-

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Abbreviations: ALT, alanine aminotransferase; CCA, common carotid artery; IMT, intima-media thickness; PPAR, peroxisome proliferator–activated receptor; TZD, thiazolidinedione.

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

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formance of ≥50% of prescribed self-glucose monitoring, fasting plasma glucose concentration ≤11.1 mmol/l (200 mg/dl) with daily insulin dose <150 units, fasting triglycerides <4.5 mmol/l (400 mg/dl), serum alanine aminotransferase (ALT) <1.5 times the upper normal limit, and consumption of ≥60% of placebo pills administered in a single-blind fashion during the last 4 weeks of the run-in phase.

Randomization and blinding

Eligible participants were randomized to daily 400 mg troglitazone or placebo. To balance treatment groups on atherosclerosis-related factors, participants were randomized to one of four strata: baseline common carotid artery (CCA)-IMT (<0.8 mm, ≥0.8 mm) and prevalent cardiovascular disease (yes/no); 0.8 mm was chosen since this value has a high positive predictive value and specificity for the presence of coronary artery disease (11). Participants, investigators, image analysts, and clinical and data coordinating center staff were blinded to treatment assignment.

Follow-up

Clinical follow-up after randomization occurred at 2 and 4 weeks, then monthly during the first 6 months, then every 2 months for the remainder of the 2-year trial. Insulin doses were adjusted to maintain fasting and premeal capillary glucose concentrations between 5.6 and 8.3 mmol/l (100–150 mg/dl). Participants with blood pressure >140/90 mmHg were given antihypertensive medication, primarily an ACE inhibitor. Participants with fasting plasma LDL cholesterol levels >4.1 mmol/l (160 mg/dl) were given lipid-lowering medication, primarily an hydroxymethylglutaryl-CoA reductase inhibitor (nicotinic acid was not used). All participants received dietary and exercise instruction (12).

Study medication was stopped if serum ALT exceeded three times the upper normal limit or HbA_{1c} (A1C) exceeded 10% on three consecutive assessments. In the former case, subjects participated in follow-up visits off study medication. In the latter case, subjects ended participation and were referred for their diabetes care. Participants provided written informed consent approved by the University of Southern California Institutional Review Board.

Laboratory methods

At each clinic visit, blood was obtained after an 8- to 12-h fast. Plasma glucose levels were measured by the glucose oxidase technique using the Beckman Glucose II analyzer (Beckman Instruments). A1C levels were measured by high-pressure liquid chromatography (BioRad Diamet). Plasma total cholesterol, total triglyceride, and HDL cholesterol concentrations were determined by enzymatic assays standardized to the Centers for Disease Control and Prevention (13). Apolipoproteins were quantified by electroimmunoassay (14).

CCA-IMT measurement

High-resolution B-mode carotid artery ultrasounds were obtained at baseline and every 6 months using an Apogee 800 Plus (Advanced Technology Laboratory) ultrasound system with a linear array 7.5-MHz transducer. The CCA was imaged along the longitudinal axis with the jugular vein juxtaposed above the carotid artery. The electrocardiogram signal and ultrasound images were simultaneously recorded on super-VHS videotape and all initial instrumentation settings recorded for subsequent examination. Each individual's baseline image was used as an online guide for follow-up examinations on a split-screen system designed for repeat image acquisition for longitudinal studies (patent pending) (15,16). The software program (Prowin, patent pending) used to analyze images utilized automated boundary detection to locate the lumen-intima and media-adventitia echo boundaries at subpixel resolution (15,16). The IMT measurement consisting of an average of 70–100 individual measurements was made along a 1-cm distance in the right distal CCA far wall. The CCA-IMT coefficient of variation was 1% for repeat ultrasounds obtained 2 weeks apart.

Sample size

The primary trial end point was rate of change in the right distal CCA far wall IMT. Power calculations required a sample size of 200 participants to detect a treatment effect size ≥0.40, with 80% power and two-sided $\alpha = 0.05$. With an anticipated 15% annual dropout rate, sample size was inflated to 288 participants.

Statistical analysis

Baseline data were obtained at the end of the run-in phase before randomization and were compared between treatment groups using either an independent samples *t* test for means or a χ^2 test for proportions.

Analysis of CCA-IMT progression was conducted for all randomized participants with baseline and at least one follow-up CCA-IMT measure. A general linear mixed-effects model regressed all CCA-IMT determinations on follow-up time, adjusting for randomization stratification factors. The regression coefficient associated with follow-up time represents the average rate of CCA-IMT change. Treatment group differences in the average rates of CCA-IMT change were tested for significance by including a treatment × follow-up time interaction term. Analyses of the primary end point were conducted in subgroups of participants defined by the CCA-IMT randomization stratification using the same mixed-effects models.

Analyses of laboratory and clinical variable changes used data from all evaluable participants and were evaluated using mixed-effects models for repeated measures. The dependent variable was the change (from baseline), measured at specified trial visits; an independent treatment group indicator variable tested for group differences in the mean change over the trial. Percentage pill compliance was computed at each visit and averaged over the trial.

Adverse events were reported for the total cohort of randomized participants. Occurrence of major cardiovascular events (fatal and nonfatal) included any of myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, peripheral vascular disease, deep-vein thrombosis, pulmonary embolus, or arterial revascularization procedures. Other clinical events reported were death and occurrence of elevated serum ALT levels. The proportions of participants experiencing events were compared between treatment groups using a two-tailed Fisher's exact test.

RESULTS

Trial profile

Of 624 prescreened participants, 473 entered the run-in phase. Over 17 months, 299 participants were randomized (150 placebo, 149 troglitazone); 66% were female, 90% were Hispanic, and <10% had clinical cardiovascular disease. Mean age at randomization was 52.4 years (range 30–70).

Of the 299 randomized participants,

Table 1—*Demographic and clinical characteristics at initial screening visit*

	Evaluable troglitazone	Evaluable placebo	*P* value*
n	142	134	
Female	95 (66.9)	91 (67.9)	0.86
Hispanic	123 (86.6)	123 (91.8)	0.17
Age (years)	52.4 ± 9.4	52.6 ± 8.7	0.82
Education (years)	7.4 ± 5.2	7.5 ± 4.2	0.94†
Duration of diabetes (years)	9.8 ± 6.2	9.7 ± 6.4	0.83
Duration of insulin therapy (years)	4.1 ± 4.3	4.1 ± 4.2	0.87
A1C (%)	9.9 ± 2.3	9.7 ± 2.2	0.47
Fasting glucose (mmol/l)	11.9 ± 4.4	11.4 ± 4.0	0.32
Daily insulin dose (units)	51.5 ± 30.0	54.5 ± 29.0	0.39
Systolic blood pressure (mmHg)	136.9 ± 19.6	134.4 ± 20.4	0.31
Diastolic blood pressure (mmHg)	80.3 ± 9.5	79.0 ± 11.0	0.28
BMI (kg/m^2)	32.1 ± 5.9	31.1 ± 6.0	0.18
Weight (lb)	183.1 ± 41.2	174.5 ± 36.7	0.07
Waist-to-hip ratio	0.94 ± 0.08	0.92 ± 0.06	0.02†
Total cholesterol (mmol/l)	5.1 ± 1.0	5.2 ± 1.1	0.58
Triglycerides (mmol/l)	1.3 ± 0.4	1.3 ± 0.4	0.28†
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.3 ± 0.4	0.65†
LDL cholesterol (mmol/l)	4.4 ± 2.2	4.7 ± 3.1	0.59

Data are means ± SD or *n* (%). **P* values from *t* test for independent samples or χ^2 test (sex and ethnicity). †*t* test for unequal variances.

108 (72%) placebo-treated and 126 (85%) troglitazone-treated completed the 2-year trial. Of 65 participants (42 placebo treated, 23 troglitazone treated) who withdrew, 42 (26 placebo treated, 16 troglitazone treated) were evaluable on the primary trial end point. Thus, a total of 276 participants (134 [89%] placebo treated, 142 [95%] troglitazone treated) were evaluable.

Prerandomization characteristics

Other than waist-to-hip ratio ($P = 0.02$), there were no treatment group differences in any parameter at the initial screening visit among the 276 evaluable participants (Table 1). Participants without evaluable CCA-IMT results ($n = 23$) were not significantly different from the evaluable subjects in any Table 1 parameter (data not shown).

In the 276 evaluable participants, the mean (±SD) values at randomization were as follows: A1C 7.5 ± 1.1%, daily insulin dose 60 ± 33 units, fasting plasma glucose 7.9 ± 2.1 mmol/l, and fasting plasma insulin 21 ± 21 μU/ml. None of these parameters differed significantly between treatment groups (Table 2).

Compared with participants in the <0.8-mm stratum at randomization, participants in the ≥0.8-mm stratum were significantly older (aged 54.9 ± 8.2 vs. 47.4 ± 8.7 years; $P < 0.0001$), had a longer duration of diabetes (10.7 ± 6.4 vs. 7.7 ± 5.4 years; $P = 0.0002$), longer duration of insulin therapy (4.5 ± 4.4 vs. 3.3 ± 4.1 years; $P = 0.04$), higher systolic blood pressure (140.2 ± 19.3 vs. 125.9 ± 17.8 mmHg; $P < 0.0001$), higher diastolic blood pressure (81.0 ± 10.4 vs. 76.8 ± 9.3 mmHg; $P = 0.001$), and higher BMI (32.2 ± 6.0 vs. 30.4 ± 5.9 kg/m^2; $P = 0.03$). Fasting lipids, glucose, A1C, and insulin dose did not differ between strata.

Characteristics during treatment

During the randomized phase of the trial, pill compliance for troglitazone- and placebo-treated participants was 95 ± 7% and 95 ± 6%, respectively ($P = 0.45$). Fasting glucose and insulin rose significantly in the placebo group (both $P < 0.0001$) but not in the troglitazone group ($P = 0.11$ and $P = 0.28$), resulting in a significant difference in glucose and insulin patterns between treatment groups (Table 2; $P < 0.0001$). A1C rose in the placebo group and fell in the troglitazone group ($P < 0.0001$ between groups). Daily insulin doses differed between groups and decreased in the troglitazone group ($P < 0.0001$ between groups). Although the change in fasting glucose in the troglitazone group was apparent in the ≥0.8-mm stratum, troglitazone had no effect on this variable in the <0.8-mm stratum (Table 3). Troglitazone-treated participants had greater BMI increases than placebo-treated participants overall (Table 2; $P < 0.0001$) and by IMT strata (Table 3; $P < 0.005$). Changes in total, LDL, and HDL cholesterol levels, triglycerides, and apolipoproteins did not differ between treatment groups overall (Table 2) or by IMT strata (Table 3).

Troglitazone-treated participants had larger diastolic blood pressure decreases than placebo-treated participants (Table 2; $P = 0.05$) that differed by treatment in the ≥0.8-mm stratum (Table 3; $P = 0.03$) and not in the<0.8-mm stratum (Table 3; $P = 0.91$). Diastolic blood pressure reductions were significantly greater in the troglitazone-treated participants in the ≥0.8-mm stratum (Table 3; $P < 0.0001$) compared with the <0.8-mm stratum (Table 3; $P = 0.06$). The same pattern was seen for systolic blood pressure (Tables 2 and 3).

Antihypertensive and lipid-lowering medications during the trial

Of 276 subjects, 184 (67%) received antihypertensive therapy and 80 (30%) received lipid-lowering medications. There was no difference in antihypertensive or lipid-lowering medication use between treatment groups or by IMT strata ($P > 0.1$). Median duration of antihypertensive and lipid-lowering medication use was 1.8 and 0.7 years, respectively, in the placebo-treated subjects and 1.9 and 0.6 years, respectively, in the troglitazone-treated subjects.

Primary end point

At randomization, evaluable participants in the troglitazone and placebo groups had similar CCA-IMT values (0.809 ± 0.139 vs. 0.821 ± 0.169 mm; $P = 0.52$). Participants in both treatment groups were followed for a median of 24 months (range 5–31; $P = 0.20$) and had a median of six CCA-IMT measurements (range 3–6; $P = 0.18$). CCA-IMT increased at a mean (±SD) rate of 0.0030 ± 0.021 mm/year in the troglitazone-treated group and 0.0066 ± 0.021 mm/year in the placebo-treated group ($P = 0.17$) (Fig. 1).

For subjects with baseline CCA-IMT ≥0.8 mm, the rate of CCA-IMT progression was significantly lower in the 97 troglitazone-treated participants than in the 91 placebo-treated participants ($P = 0.03$; Fig. 1). For subjects with baseline CCA-IMT <0.8 mm, the rate of CCA-IMT progression was nonsignificantly greater in the 45 troglitazone than in the 43 pla-

Table 2—*Laboratory and clinical parameters at randomization and changes during treatment in all participants with evaluable carotid IMT results*

Variable	Troglitazone	Placebo	*P* value*
Fasting glucose (mg/dl)			
Randomization	140 (137.9 ± 34.9)	133 (146.0 ± 39.9)	0.08
Change	140 (−3.3 ± 24.8)	133 (11.6 ± 24.8)	<0.0001†
P value‡	0.11	<0.0001	
A1C (%)			
Randomization	142 (7.6 ± 1.0)	132 (7.5 ± 1.1)	0.72
Change	142 (−0.3 ± 1.2)	132 (0.2 ± 1.1)	<0.0001
P value‡	0.0001	0.003	
Insulin dose (units)			
Randomization	142 (59.1 ± 31.0)	134 (61.3 ± 35.8)	0.58
Change	132 (−15.5 ± 16.1)	126 (3.3 ± 16.8)	<0.0001
P value‡	<0.0001	0.03	
Fasting insulin (μU/ml)			
Randomization	140 (21.8 ± 22.0)	133 (20.2 ± 19.7)	0.53
Change	126 (1.3 ± 14.6)	113 (9.0 ± 13.8)	<0.0001
P value‡	0.28	<0.0001	
Total cholesterol (mg/dl)			
Randomization	141 (169.1 ± 32.2)	133 (173.1 ± 36.0)	0.33
Change	141 (12.2 ± 20.2)	133 (12.0 ± 20.8)	0.95
P value‡	<0.0001	<0.0001	
LDL cholesterol (mg/dl)			
Randomization	140 (98.8 ± 28.5)	133 (98.9 ± 31.1)	0.99
Change	140 (6.8 ± 16.6)	133 (5.7 ± 17.3)	0.58
P value‡	<0.0001	0.0001	
HDL cholesterol (mg/dl)			
Randomization	141 (44.1 ± 10.1)	133 (45.3 ± 13.3)	0.39§
Change	141 (5.6 ± 8.3)	133 (4.1 ± 8.1)	0.14
P value‡	<0.0001	<0.0001	
Triglycerides (mg/dl)			
Randomization	141 (131.6 ± 75.6)	132 (145.2 ± 95.3)	0.19§
Change	140 (−5.2 ± 49.7)	131 (5.0 ± 49.2)	0.09
P value‡	0.21	0.25	
Apolipoprotein A-I (mg/dl)			
Randomization	140 (110.9 ± 21.6)	134 (117.6 ± 26.0)	0.02§
Change	140 (9.2 ± 11.8)	134 (10.0 ± 11.6)	0.54†
P value‡	<0.0001	<0.0001	
Apolipoprotein B (mg/dl)			
Randomization	140 (94.6 ± 19.2)	134 (98.3 ± 19.1)	0.12
Change	140 (−1.8 ± 10.6)	134 (−1.7 ± 10.4)	0.93
P value‡	0.047	0.07	
Apolipoprotein C-III (mg/dl)			
Randomization	140 (10.7 ± 3.7)	134 (12.5 ± 6.0)	0.003§
Change	140 (0.5 ± 3.5)	134 (0.2 ± 3.5)	0.41†
P value‡	0.07	0.56	
Systolic blood pressure (mmHg)			
Randomization	142 (130.6 ± 19.2)	134 (131.2 ± 18.9)	0.81
Change	142 (−2.4 ± 10.7)	134 (−0.7 ± 10.4)	0.18
P value‡	0.008	0.47	
Diastolic blood pressure (mmHg)			
Randomization	142 (76.3 ± 8.8)	134 (76.0 ± 10.1)	0.81
Change	142 (−3.3 ± 6.0)	134 (−1.8 ± 6.9)	0.05
P value‡	<0.0001	0.001	
Weight (kg)			
Randomization	142 (83.8 ± 18.3)	134 (80.4 ± 16.6)	0.11
Change	142 (3.3 ± 3.6)	134 (1.5 ± 3.5)	<0.0001
P value‡	<0.0001	<0.0001	
BMI (kg/m^2)			
Randomization	142 (32.4 ± 5.9)	134 (31.6 ± 6.0)	0.26
Change	142 (1.3 ± 1.2)	134 (0.6 ± 1.2)	<0.0001
P value‡	<0.0001	<0.0001	

Data are *n* (means ± SD). **P* values from *t* test for independent samples for values at randomization or from mixed-effects model for on-trial changes. †*P* value from mixed effects model, adjusting for randomization levels. ‡*P* value testing that on-trial changes differ from zero from mixed-effects models. §*t* test for unequal variances.

cebo participants ($P = 0.26$) (Fig. 1). Treatment group effects on CCA-IMT progression significantly differed between IMT randomization strata ($P = 0.04$). Within each treatment group, CCA-IMT progression did not significantly differ by IMT strata ($P = 0.15$ for troglitazone treated, $P = 0.14$ for placebo treated), possibly due to reduced power. In a secondary analysis of the primary trial end point, results were similar when limited to subjects with at least 18 months of follow-up.

Adverse and clinical events

Eleven participants (six troglitazone and five placebo; $P = 0.77$) were withdrawn from treatment when they developed ALT more than three times the upper normal limit. Twelve participants had at least one cardiovascular event during the trial (six troglitazone and six placebo; $P = 1.00$). Events included one fatal and four nonfatal myocardial infarctions (three troglitazone and two placebo), five cerebrovascular accidents (two troglitazone and three placebo), two unstable anginas (one troglitazone and one placebo), and one pulmonary embolus (troglitazone).

CONCLUSIONS — Although PPARγ agonist therapy in addition to standard diabetes care for 2 years reduced subclinical atherosclerosis progression by >50% in the entire Troglitazone Atherosclerosis Regression Trial cohort, this did not reach statistical significance. However, PPARγ agonist therapy significantly reduced subclinical atherosclerosis progression relative to placebo in participants with baseline CCA-IMT ≥0.8 mm (Fig. 1). Thus, troglitazone had a beneficial effect on the reduction of subclinical atherosclerosis in middle-aged, well-controlled, insulin-treated type 2 diabetic patients with a baseline CCA-IMT ≥0.8 mm. Generalizability of these results may be limited, however, since 90% of the cohort was Hispanic and had a low level of education.

Reasons for the disparate effects of troglitazone on IMT progression in participants with baseline CCA-IMT ≥0.8 mm vs. <0.8 mm are not clear. However, the changes in fasting glucose, A1C, and blood pressure with troglitazone were more apparent in participants with baseline CCA-IMT ≥0.8 mm. At the cellular level, PPARγ activation has both antiatherogenic and proatherogenic properties. Activation of this receptor inhibits processes critical for atherogenesis, in-

Table 3—*Laboratory and clinical parameters at randomization and changes during treatment in participants with evaluable carotid IMT results by baseline IMT strata*

Variable	Troglitazone	Placebo	*P* value*
Fasting glucose (mg/dl)			
IMT <0.8 mm			
Randomization	45 (140.5 ± 35.5)	43 (140.8 ± 32.4)	0.97
Change	45 (5.4 ± 33.5)	43 (11.1 ± 33.4)	0.42
P value†	0.28	0.03	
IMT ≥0.8 mm			
Randomization	95 (136.7 ± 34.7)	90 (148.5 ± 42.9)	0.04‡
Change	95 (−7.1 ± 24.4)	90 (12.6 ± 24.7)	<0.0001§
P value†	0.004	<0.0001	
A1C (%)			
IMT <0.8 mm			
Randomization	45 (7.7 ± 1.1)	43 (7.3 ± 1.2)	0.18
Change	45 (−0.2 ± 0.7)	43 (0.4 ± 0.7)	0.007
P value†	0.25	0.009	
IMT ≥0.8 mm			
Randomization	97 (7.5 ± 1.0)	89 (7.6 ± 1.1)	0.55
Change	97 (−0.3 ± 1.0)	89 (0.1 ± 0.9)	<0.0001
P value†	<0.0001	0.10	
Insulin dose (units)			
IMT <0.8 mm			
Randomization	45 (62.0 ± 34.3)	43 (58.0 ± 33.5)	0.58
Change	44 (−15.3 ± 17.9)	43 (2.0 ± 18.4)	<0.0001
P value†	<0.0001	0.47	
IMT ≥0.8 mm			
Randomization	97 (63.7 ± 29.4)	91 (70.6 ± 36.9)	0.29
Change	96 (−15.6 ± 16.6)	91 (3.8 ± 16.2)	<0.0001
P value†	<0.0001	0.02	
Fasting insulin (μU/ml)			
IMT <0.8 mm			
Randomization	45 (16.0 ± 15.1)	43 (17.1 ± 12.1)	0.72
Change	40 (2.9 ± 8.2)	36 (9.2 ± 8.4)	0.002
P value†	0.03	<0.0001	
IMT ≥0.8 mm			
Randomization	95 (24.6 ± 24.1)	90 (21.8 ± 22.3)	0.41
Change	86 (0.6 ± 15.8)	77 (9.0 ± 15.8)	0.001
P value†	0.71	<0.0001	
Total cholesterol (mg/dl)			
IMT <0.8 mm			
Randomization	45 (168.5 ± 28.8)	43 (169.5 ± 38.1)	0.89
Change	45 (15.5 ± 23.5)	43 (14.1 ± 23.6)	0.78
P value†	<0.0001	<0.0001	
IMT ≥0.8 mm			
Randomization	96 (169.3 ± 33.8)	90 (174.8 ± 35.0)	0.28
Change	96 (10.6 ± 18.6)	90 (11.1 ± 19.0)	0.88
P value†	<0.0001	<0.0001	
LDL cholesterol (mg/dl)			
IMT <0.8 mm			
Randomization	45 (99.0 ± 28.6)	43 (94.4 ± 31.8)	0.48
Change	45 (7.4 ± 18.1)	43 (6.8 ± 17.7)	0.87
P value†	0.006	0.01	
IMT ≥0.8 mm			
Randomization	95 (98.8 ± 28.6)	90 (101.0 ± 30.7)	0.60
Change	95 (6.6 ± 16.6)	90 (5.2 ± 16.1)	0.57
P value†	0.0001	0.003	

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Table 3—*Continued*

Variable	Troglitazone	Placebo	*P* value*
HDL cholesterol (mg/dl)			
IMT <0.8 mm			
Randomization	45 (44.1 ± 10.3)	43 (45.0 ± 10.3)	0.66
Change	45 (5.4 ± 6.0)	43 (4.6 ± 5.9)	0.53
P value†	<0.0001	<0.0001	
IMT ≥0.8 mm			
Randomization	96 (44.1 ± 10.1)	90 (45.4 ± 14.5)	0.45‡
Change	96 (5.8 ± 9.8)	90 (3.9 ± 9.5)	0.19
P value†	<0.0001	0.0001	
Triglycerides (mg/dl)			
IMT <0.8 mm			
Randomization	45 (130.0 ± 80.3)	42 (128.1 ± 59.0)	0.90‡
Change	44 (−1.1 ± 45.1)	41 (13.9 ± 45.5)	0.13
P value†	0.87	0.051	
IMT ≥0.8 mm			
Randomization	96 (132.4 ± 73.6)	90 (153.2 ± 107.5)	0.13‡
Change	96 (−7.1 ± 50.9)	90 (0.7 ± 51.2)	0.30
P value†	0.17	0.90	
Apolipoprotein A-I (mg/dl)			
IMT <0.8 mm			
Randomization	44 (108.2 ± 21.6)	43 (117.2 ± 24.6)	0.07
Change	44 (8.5 ± 12.6)	43 (8.6 ± 12.8)	0.98§
P value†	<0.0001	<0.0001	
IMT ≥0.8 mm			
Randomization	96 (112.1 ± 21.6)	91 (117.7 ± 26.8)	0.11
Change	96 (10.5 ± 15.7)	91 (8.8 ± 15.3)	0.52
P value†	<0.0001	<0.0001	
Apolipoprotein B (mg/dl)			
IMT <0.8 mm			
Randomization	44 (92.9 ± 18.0)	43 (95.4 ± 18.0)	0.51
Change	44 (0.2 ± 9.9)	43 (−1.0 ± 9.8)	0.58
P value†	0.91	0.50	
IMT ≥0.8 mm			
Randomization	96 (95.4 ± 19.7)	91 (99.7 ± 19.6)	0.15
Change	96 (−2.7 ± 10.8)	91 (−2.0 ± 10.5)	0.67
P value†	0.02	0.09	
Apolipoprotein C-III (mg/dl)			
IMT <0.8 mm			
Randomization	44 (10.5 ± 2.9)	43 (12.3 ± 6.4)	0.10‡
Change	44 (1.2 ± 4.6)	43 (0.8 ± 4.6)	0.33
P value†	0.09	0.24	
IMT ≥0.8 mm			
Randomization	96 (10.8 ± 4.0)	91 (12.6 ± 5.9)	0.01‡
Change	96 (0.06 ± 2.0)	91 (−0.01 ± 1.9)	0.82§
P value†	0.78	0.96	
Systolic blood pressure (mmHg)			
IMT <0.8 mm			
Randomization	45 (120.5 ± 16.1)	43 (123.0 ± 19.3)	0.51
Change	45 (0.9 ± 10.1)	43 (−0.1 ± 9.8)	0.63
P value†	0.53	0.96	
IMT ≥0.8 mm			
Randomization	97 (135.3 ± 18.7)	91 (135.1 ± 17.6)	0.92
Change	97 (−3.9 ± 10.8)	91 (−0.9 ± 10.5)	0.06
P value†	0.0004	0.40	

Continued on following page

Table 3—*Continued*

Variable	Troglitazone	Placebo	*P* value*
Diastolic blood pressure (mmHg)			
IMT <0.8 mm			
Randomization	45 (73.3 ± 8.3)	43 (73.2 ± 9.4)	0.95
Change	45 (−1.6 ± 6.0)	43 (−1.5 ± 5.9)	0.91
P value†	0.063	0.10	
IMT ≥0.8 mm			
Randomization	97 (77.7 ± 8.7)	91 (77.4 ± 10.1)	0.82
Change	97 (−4.1 ± 6.9)	91 (−1.9 ± 6.7)	0.03
P value†	<0.0001	0.006	
Weight (kg)			
IMT <0.8 mm			
Randomization	45 (80.1 ± 2.7)	43 (76.4 ± 2.6)	0.31
Change	45 (3.9 ± 4.0)	43 (1.5 ± 3.9)	0.002
P value†	<0.0001	0.009	
IMT ≥0.8 mm			
Randomization	97 (85.7 ± 1.9)	91 (82.5 ± 1.7)	0.20
Change	97 (3.0 ± 3.9)	91 (1.5 ± 3.8)	0.007
P value†	<0.0001	<0.0001	
BMI (kg/m^2)			
IMT <0.8 mm			
Randomization	45 (31.7 ± 6.0)	43 (30.6 ± 6.0)	0.37
Change	45 (1.6 ± 1.3)	43 (0.7 ± 1.3)	0.005
P value†	<0.0001	0.005	
IMT ≥0.8 mm			
Randomization	97 (32.7 ± 0.6)	91 (32.1 ± 0.6)	0.55
Change	97 (1.2 ± 1.0)	91 (0.6 ± 9.5)	0.003
P value†	<0.0001	<0.0001	

Data are *n* (means ± SD). **P* value from *t* test for independent samples for values at randomization or from mixed-effects model for on-trial changes. †*P* value testing that on-trial changes differ from zero from mixed-effects models. ‡*t* test for unequal variances. §*P* value from mixed-effects model, adjusting for randomization levels.

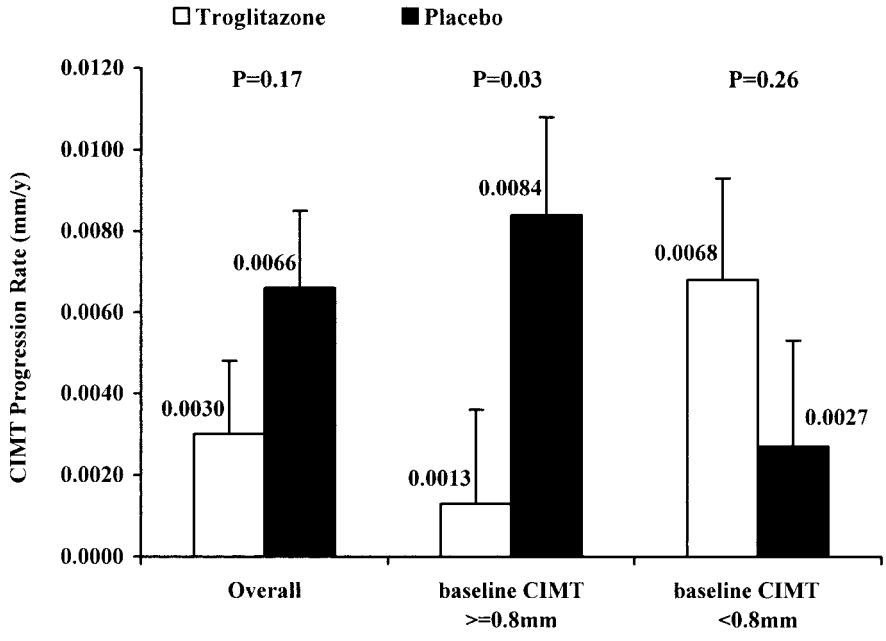

Figure 1—*Effect of troglitazone versus placebo on the progression of carotid artery intima-media thickness overall and stratified by baseline carotid artery intima-media thickness.*

cluding inflammatory cytokine production, cellular proliferation and migration, and expression of cellular adhesion molecules. In contrast, PPARγ activation stimulates conversion of macrophages into foam cells by promoting uptake of lipids by the CD36 scavenger receptor, a proatherogenic process (17). Macrophage content in the intima is greatest in the early stages of atherosclerosis, making the arterial wall more vulnerable to any proatherogenic effects of troglitazone. Thus, the net effect of troglitazone in the combined cohort of subjects with less (CCA-IMT <0.8 mm) and more (CCA-IMT ≥0.8 mm) atherosclerosis at baseline may be a result of competing pro- and antiatherogenic effects in individuals with different stages or activity of atherosclerosis. These results reflect the growing body of literature that demonstrates a considerable heterogeneity of cardiovascular disease response to TZDs (18,19).

Our results differ from two previous reports in type 2 diabetic patients that indicated short-term therapy with troglitazone (9) or pioglitazone (10) reduced

IMT. Sample size and the specific population studied (Japanese) may account for differences between studies, as could the fact that we maintained relatively low-risk lipid and blood pressure values in our subjects (97% of the cohort was taking lipid-lowering and/or antihypertensive medication) and tight diabetes control with insulin therapy. Intensified insulin therapy (reduction of A1C levels from 9.6 to 7.1% at the end of the run-in phase) as accomplished in this trial has been shown to reduce carotid IMT in type 1 diabetic subjects (20). The lack of lipid and apoprotein differences between treatment groups in this trial is likely a result of the intensive diabetes control and lipid-lowering therapy. The relatively lower progression rate in this trial relative to previous studies most likely reflects the tighter diabetes and risk factor control.

Although mechanisms for excess atherosclerosis risk in type 2 diabetes have not been elucidated, insulin dosage (21), hyperinsulinemia (22), insulin sensitivity (23), and hyperglycemia (24) have been variably related to carotid artery IMT. The present study could not single out any of these factors as a potential mediator of IMT reduction seen with troglitazone in the subjects with CCA-IMT ≥0.8 mm. Overall and in that subset, troglitazone-treated subjects had a significantly greater reduction in exogenous insulin requirements, significantly lower on-trial serum insulin concentration and better glycemic control than the placebo-treated group. In addition, both systolic and diastolic blood pressures were lower in the troglitazone- than the placebo-treated subjects in the ≥0.8-mm stratum; there were no differences in blood pressure between treatment groups in the <0.8-mm stratum. These differences were small but together could have had an important impact on IMT progression. The fact that the differences in atherosclerosis risk factors occurred despite our attempts to target the factors into the same range demonstrates a potential benefit of insulin plus TZD therapy over aggressive insulin treatment alone in type 2 diabetes.

More than a million diabetic subjects currently take TZDs, and the increasing incidence of type 2 diabetes predicts that the number of individuals using insulin sensitizers will grow. Although troglitazone (the first TZD to be marketed) has been replaced by other TZDs, the results of this trial have direct and important implications for diabetic patients using TZDs. The growing data suggest that PPARγ activation exerts antiatherogenic effects; however, further trials will have to be conducted with other TZDs to determine whether the antiatherogenic effect of these products is a class effect. We have already demonstrated in insulin-resistant nondiabetic young women without preexisting cardiovascular disease that TZD therapy reduces the progression of atherosclerosis (25). A similar finding of reduced IMT progression was reported in nondiabetic individuals with coronary heart disease (26). Together, these results suggest that PPARγ agonists may play an important role in reducing the progression of subclinical atherosclerosis not only in type 2 diabetes but also in nondiabetic individuals who are at high risk for atherosclerosis. The present study demonstrates that the effects of TZD therapy on subclinical atherosclerosis progression are not uniform among individuals.

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