Effect of Rosiglitazone on Common Carotid Intima-Media Thickness Progression in Coronary Artery Disease Patients Without Diabetes Mellitus

Jagdip S. Sidhu, Zoltan Kaposzta, Hugh S. Markus, Juan Carlos Kaski

Objectives—Thiazolidinediones, such as rosiglitazone, have been shown to retard atherosclerosis disease progression in diabetic subjects. These agents may have anti-atherosclerotic effects through direct inhibition of inflammatory processes in the vessel wall, and so their benefit may extend to patients with atherosclerotic disease, even in the absence of diabetes. In this study, we assessed the effect of rosiglitazone on common carotid intima-media thickness (IMT) progression in nondiabetic coronary artery disease (CAD) patients.

Methods and Results—Consecutive subjects (n=92) with clinically stable, angiographically documented CAD and without diabetes mellitus were randomized in a double-blind manner to receive placebo or rosiglitazone for 48 weeks. They received single-dose placebo and rosiglitazone 4 mg daily for the initial 8 weeks, and the doses were doubled for the remainder of the study. Common carotid IMT together with fasting glucose, insulin, and lipid profile were measured at baseline and repeated after 24 and 48 weeks. Rosiglitazone-treated patients showed reduced IMT progression compared with the placebo group, −0.012 mm/48 weeks versus 0.031 mm/48 weeks (P=0.03). Rosiglitazone treatment significantly reduced insulin resistance, estimated by homeostasis model of insulin resistance index, compared with placebo (P=0.01).

Conclusions—Rosiglitazone reduces common carotid IMT progression in nondiabetic CAD patients, and insulin-sensitization may be one contributory mechanism. (Arterioscler Thromb Vasc Biol. 2004;24:930-934.)

Key Words: PPAR-γ agonists ■ thiazolidinediones ■ carotid intima-media thickness ■ coronary artery disease.

The thiazolidinedione rosiglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, is an insulin-sensitizing agent and is used in the treatment of type 2 diabetes mellitus. Data suggest that these agents may also retard atherosclerotic disease progression. Thiazolidinediones have been shown to reduce atherosclerotic lesion area in mouse models of atherosclerosis that exhibit hyperlipidemia and insulin-resistance.1-3 Thiazolidinediones have also been reported to reduce common carotid arterial intima-media thickness (IMT) progression, a surrogate index of atherosclerotic disease progression, in type 2 diabetic subjects.4-5 These results taken together suggest that insulin sensitization and glucose-lowering are important mechanisms underlying the antiatherogenic effects of these agents.1-5

However, recent evidence suggests that PPAR-γ agonists may also inhibit atherosclerotic disease progression by exerting anti-inflammatory effects within the artery wall.6-7 Therefore, the potential antiatherogenic effects of PPAR-γ agonists may not be confined to type 2 diabetic patients.8 The PPAR-γ agonist troglitazone has been shown to retard atherosclerotic lesion formation and macrophage accumulation in plaques in nondiabetic low-density lipoprotein (LDL) receptor-deficient mice.9 We recently found that rosiglitazone reduces circulating markers of inflammation, such as C-reactive protein, in nondiabetic patients with coronary artery disease (CAD).10 In the present study, we measured the effect of treatment on common carotid IMT progression, a noninvasive surrogate marker of atherosclerotic disease progression, in nondiabetic CAD patients.11-12

Methods

Study Patients

Consecutive patients with stable CAD were recruited from our hospital clinics. Inclusion criteria were angiographically documented CAD (≥50% lumen diameter reduction of at least 1 major coronary artery according to 2 independent observers) and age younger than 75 years. Patients with any of the following were excluded: previous diagnosis of diabetes mellitus reported by family practitioner or hospital physician, a history of acute coronary syndrome or revascularization in the previous 3 months, rest angina, cardiac failure (NYHA class I to IV), malignant or hematological diseases, concurrent anticoagulant or antiplatelet therapy other than aspirin, baseline
alcohol transaminase >2-times the upper limit of normal, or known hypersensitivity to rosiglitazone. The study was approved by the local ethics research committee and all subjects gave written informed consent before enrollment.

Subjects were randomized (double-blind) to receive placebo or rosiglitazone for 48 weeks. They received single-dose placebo and rosiglitazone 4 mg once per day for the initial 8 weeks and, after checking serum transaminases, the doses were doubled for the remaining 40 weeks of the study. All other cardiovascular medications remained unchanged during the study. Rosiglitazone and matching placebo tablets were supplied by GlaxoSmithKline (UK). Compliance assessed by tablet count was >95%.

Study Protocol
Patients underwent baseline common carotid artery (CCA) scanning in a fasting state in the morning. Blood samples were also collected, before scanning, for measurement of electrolytes, liver function tests, lipid profile, serum insulin, and plasma glucose. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure was measured using a standard sphygmomanometer (Omron 705CP). All measurements were repeated after 24 and 48 weeks of treatment, except for fasting insulin, which was repeated after 24 weeks only.

Biochemical Parameters
All biochemical measurements were performed by the biochemistry department of our institution, with the use of standard methods. The LDL cholesterol was calculated according to the Friedewald equation. Serum insulin was measured by immunonassay (Elecsys; Roche Diagnostics). The homeostasis model of insulin resistance index (HOMA-R) was used as a measure of insulin resistance, where HOMA-R = fasting serum insulin (µU/mL) × fasting plasma glucose (mmol/L) ÷ 22.5.14

Common Carotid IMT
Vascular studies were performed by a single operator (J.S.S.). Common carotid artery imaging was performed with an ATL HDI 3000 ultrasound system by use of a 5- to 12-MHz linear transducer. All ultrasonic examinations were stored on a super VHS video system for subsequent offline processing. Settings for depth-gain compensation, preprocessing, persistence, and postprocessing were held constant. Video images were captured in end-diastole of the cardiac cycle by triggering to the ECG. The frozen video images were digitized and transferred for further analysis to a personal computer. Images were analyzed with the technician blinded to patient identity and treatment group. Mean CCA IMT was measured in the far wall over the distal 2-cm segment of the common carotid, defined by the carotid flow divider, on both sides. Far wall measurements were chosen in accordance with methodological recommendations because the far wall is more easily and consistently visualized than the near wall.15 Mean IMT was measured by using a semi-automated computer analysis system that detects the lumen/intima borderline and the media/adventitia borderline with the use of a gray value algorithm. Differences between these 2 borders were measured along a line orthogonal to the arterial wall. Single IMT values were obtained from pixel-to-pixel measurements on neighboring lines perpendicular to the vertical line and then averaged and expressed as the mean IMT for that segment. For each patient, the mean CCA IMT was computed as the average IMT on both sides. The primary outcome measure was the annualized progression slope of the mean CCA IMT (mm/year). The secondary outcome was the absolute change in mean CCA IMT from baseline at week 48 (mm). To assess reproducibility of measurements, 13 subjects had repeated scans performed by the same operator (J.S.S.) separated by 1 to 2 weeks. The mean of the absolute difference between the paired mean CCA IMT measurements was 0.047±0.028 mm, and the intraclass correlation coefficient was 0.86, which compares favorably with that reported in previous studies.15

Statistical Analysis
Results are presented as mean±1 SD for continuous variables and as percentages for categorical data. Differences in continuous variables between the treatment groups were assessed using unpaired Student t test; categorical variables were compared using Fisher exact test or χ² test. The slope of mean CCA IMT was computed for each patient from all serial ultrasound data by least-squares regression. Mean slopes were compared between treatments using analysis of covariance (ANCOVA), adjusting for baseline CCA IMT. The analysis included all patients with an evaluable slope, ie, those who had baseline ultrasound scans and at least 1 subsequent examination. One-way analysis of variance (ANOVA) for repeated measurements was used to assess the effect of treatment on measured blood parameters at each time interval; P<0.05 was considered to be statistically significant, and all reported P values are 2-sided. Statistical analysis was performed with SPSS 10.01 software, and the statistical team of the sponsor was involved in final data analysis. The total sample size was based on the size of previous similar studies with thiazolidinediones in diabetic subjects.4,5

Results
Baseline Characteristics
Of 92 patients initially enrolled in the study and randomized to each treatment group, 80 patients took the assigned treatment for a full 48 weeks, 41 in the placebo group and 39 in the rosiglitazone group (Figure 1). Five patients were unable/unwilling to attend follow-up, 4 patients with baseline fasting plasma glucose >7 mmol/L (WHO criteria for diabetes mellitus) were excluded from the study soon after randomization, and 3 patients withdrew because of side effects. Of the latter, 2 were using rosiglitazone and experienced dizziness and weight gain, respectively, whereas the remaining patient (using placebo) had dizziness. There were no other adverse events or biochemical side effects; in particular, there was not any elevation in liver transaminases. The 82 patients who had evaluable progression slopes (42 placebo, 40 rosiglitazone) were included in the primary efficacy analysis (Figure 1). Baseline characteristics (Table 1) were similar in both treatment groups, with no statistically significant differences between groups.

Ultrasonographically Determined Carotid Atherosclerosis Progression
Rosiglitazone-treated patients showed decreased mean CCA IMT progression compared with the placebo group. The baseline-adjusted mean CCA IMT progression slope was 0.031 mm/48 weeks in the placebo group versus −0.012 mm/48 weeks in the rosiglitazone group (P=0.03,
Glucose and Lipid Metabolism

The metabolic effects of rosiglitazone treatment compared with placebo are summarized in Table 2. Rosiglitazone treatment did not significantly alter fasting glucose levels at any time interval. HOMA-R decreased significantly in the rosiglitazone group compared with the placebo group ($P=0.01$, Table 2). After 24 weeks, HOMA-R had decreased from 2.64±1.80 to 2.09±1.40 U in the rosiglitazone group, whereas HOMA-R increased in the placebo group. After 24 weeks, the rosiglitazone group showed significant increases in total cholesterol ($P=0.01$) and triglyceride levels ($P=0.02$) whereas LDL levels tended to increase, although the change in LDL cholesterol failed to reach statistical significance ($P=0.08$). However, total cholesterol, LDL cholesterol, and triglyceride levels decreased in the rosiglitazone group between 24 and 48 weeks of therapy, such that there was no significant difference observed between placebo and rosiglitazone groups by the end of the study (Table 2). There was no significant treatment effect on high-density lipoprotein (HDL) levels or body mass index (Table 2). Systolic and diastolic blood pressures remained unchanged in both groups during the study (data not shown).

Discussion

This is the first study to date, to our knowledge, to assess the effect of PPAR-γ activation with rosiglitazone on CCA IMT progression in nondiabetic CAD patients. We found that rosiglitazone-treated patients showed a significant decrease in IMT progression over a treatment period of 48 weeks. Even in our nondiabetic cohort of patients, rosiglitazone treatment produced a significant reduction in insulin resistance.

Insulin resistance and hyperinsulinemia represent major risk factors for atherogenesis and atherosclerotic disease complications. Inulin resistance was shown to be associated with increased carotid IMT, in diabetic and nondiabetic subjects, in the Atherosclerosis Risk in Communities Study. Thiazolidinediones have been reported to significantly reduce carotid IMT progression in type 2 diabetic patients within a treatment period of 3 months. Although improvement in glycemic control was proposed to be a likely underlying mechanism in these studies, indices of insulin sensitivity were not measured. A study in obese subjects reported that subjects who underwent a weight loss program showed reduced carotid IMT progression in addition to improved insulin sensitivity. This study, taken together with data from our study, suggests that insulin sensitization may be one mechanism by which thiazolidinediones retard atherogenesis. However, our study was not powered to examine the association between change in insulin resistance and change in CCA IMT in the treatment group, and further studies are needed to determine whether the 2 effects of rosiglitazone are mechanistically linked.
We also observed an initial elevation in total cholesterol, LDL, and triglyceride levels in the rosiglitazone group after 24 weeks of treatment. However, this effect was not sustained and lipid levels decreased by 48 weeks, such that there was no significant difference between groups by the end of the study. High-serum LDL level is a strong predictor of carotid IMT progression, and LDL lowering has been shown to retard carotid IMT progression even in patients with moderate-to-no reduction in LDL cholesterol levels. It remains speculative as to whether reducing vessel wall inflammation retards atherosclerotic disease progression. Of relevance, in a study with hypercholesterolemic patients, pravastatin retarded carotid IMT progression even in patients with moderate-to-no reduction in LDL cholesterol levels. This implies that pleiotropic effects of pravastatin on vascular inflammation might produce beneficial effects on IMT progression.

In our study cohort, nearly all patients were using a statin and nearly half were using beta-blocker therapy at enrollment. Both of these therapies have been shown to retard carotid IMT progression, and our findings suggest that rosiglitazone may have an additive effect. Also, in support of the validity of our study, the CCA IMT progression rate in the placebo group was very similar to that reported by a previous study in CAD patients.

### Conclusion

Our results show that rosiglitazone has an inhibitory effect on CCA IMT progression, a surrogate index of atherosclerotic disease progression, in nondiabetic CAD patients. Insulin sensitization and/or direct anti-inflammatory effects may underlie this beneficial effect.

### Acknowledgments

This study was funded by an educational grant from GlaxoSmithKline (UK).

### References


### Table 2. Effect of Placebo and Rosiglitazone Treatment on Metabolic Parameters

<table>
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<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Rosiglitazone</th>
<th>( P )</th>
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<tr>
<td>Glucose, mmol/L</td>
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<td>Baseline</td>
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<td>24 wk</td>
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<td>HOMA-R, units</td>
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<td>24 wk</td>
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<td>Total cholesterol, mmol/L</td>
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<td>Triglycerides, mmol/L</td>
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Plus–minus values are means±SD. \( P \) values indicate significance of effect of treatment on variable, by ANOVA for repeated measurements, at each time interval. HOMA-R indicates homeostasis model of insulin resistance index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.


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