Troglitazone Reduces Neointimal Tissue Proliferation After Coronary Stent Implantation in Patients With Non–Insulin Dependent Diabetes Mellitus

A Serial Intravascular Ultrasound Study

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OBJECTIVES
The aim of the present study was to determine whether troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non–insulin dependent diabetes mellitus (NIDDM).

BACKGROUND
Increased in-stent restenosis in patients with diabetes mellitus is due to accelerated neointimal tissue proliferation after coronary stent implantation. Troglitazone inhibits intimal hyperplasia in experimental animal models.

METHODS
We studied 62 stented lesions in 52 patients with plasma glucose levels (PG) ≥11.1 mmol/liter at 2 h after 75 g oral glucose load. The study patients were randomized into two groups: the troglitazone group of 25 patients with 29 stents, who were treated with 400 mg of troglitazone, and the control group of 27 patients with 33 stents. All patients underwent oral glucose tolerance tests before and after their six-month treatment period. The sum of PG (ΣPG) and the sum of insulin levels (ΣIRI) were measured. Serial (postintervention and at six-month follow-up) intravascular ultrasound studies were performed. Cross-sectional images within stents were taken at every 1 mm, using an automatic pullback. Stent areas (SA), lumen areas (LA), and intimal areas (IA = SA – LA) were measured and averaged over a number of selected image slices. The intimal index was calculated as intimal index = averaged IA/averaged SA × 100%.

RESULTS
There were no differences between the two groups before treatment in ΣPG (31.35 ± 3.07 mmol/liter vs. 32.89 ± 4.87 mmol/liter, respectively, p = 0.2998) and ΣIRI (219.6 ± 106.2 mU/liter vs. 209.2 ± 91.6 mU/liter, respectively, p = 0.8934). However, reductions in ΣPG at the six-month follow-up in the troglitazone group were significantly greater than those in the control group (−21.4 ± 8.8% vs. −4.5 ± 7.4%, respectively, p < 0.0001). Likewise, decreases in ΣIRI were greater in the troglitazone-treated group (−31.4 ± 17.9% vs. −1.9 ± 15.1%, respectively, p < 0.0001). Although, there were no differences between the two groups in SA at postintervention (7.4 ± 2.2 mm² vs. 7.3 ± 1.7 mm², respectively, p = 0.9482) and at follow-up (7.3 ± 2.3 mm² vs. 7.3 ± 1.8 mm², respectively, p = 0.2307), the LA at follow-up in the troglitazone group was significantly greater than that in the control group (5.3 ± 1.7 mm² vs. 3.7 ± 1.7 mm², respectively, p = 0.0002). The IA at follow-up in the troglitazone group was significantly smaller than that in the control group (2.0 ± 0.9 mm² vs. 3.5 ± 1.8 mm², respectively, p < 0.0001). This was also true for intimal index (27.1 ± 11.5% vs. 49.0 ± 14.4%, respectively, p < 0.0001).

CONCLUSIONS
Serial intravascular ultrasound assessment shows that administration of troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with NIDDM.

(J Am Coll Cardiol 2000;36:1529–35) © 2000 by the American College of Cardiology

Although coronary stent implantation has been shown to reduce restenosis rates compared with balloon angioplasty, in-stent restenosis remains a significant clinical problem, especially in patients with diabetes mellitus (DM) (1–4). A recent study using serial intravascular ultrasound (IVUS) showed that increased restenosis in DM is due to exaggerated neointimal tissue proliferation after coronary stent implantation (5). It has been reported that troglitazone, a novel insulin-sensitizing agent, inhibits vascular smooth muscle cell growth in experimental models (6–9). However, the effect of troglitazone on neointimal tissue proliferation after coronary stent implantation was unclear. Therefore, we attempted to determine by means of serial IVUS studies whether troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non–insulin dependent diabetes mellitus (NIDDM).

METHODS

Study patients. From September 1997 through February 1999, a total of 187 patients with 244 lesions underwent coronary stent implantation using Palmaz-Schatz coronary stents (Johnson & Johnson) and MultiLink stents (Ad-
plasma glucose level (PG) based on the World Health Organization criteria (10): a with NIDDM were studied. Inclusion into the study was Kobe General Hospital. Sixty-eight lesions from 55 patients advanced Cardiovascular System, Temecula, California) in

vanced Cardiovascular System, Temecula, California) in Kobe General Hospital. Sixty-eight lesions from 55 patients with NIDDM were studied. Inclusion into the study was based on the World Health Organization criteria (10): a plasma glucose level (PG) ≥11.1 mmol/liter (200 mg/dL) at 2 h after 75 g oral glucose load. Exclusions in this study included: 1) patients with previously treated DM (oral hypoglycemic agents or insulin); 2) patients with fasting PG ≥7.77 mmol/liter (140 mg/dL); 3) patients with liver or renal dysfunction; 4) ostial lesions or bifurcational lesions; 5) lesions with reference vessel diameter <2.5 mm; 6) lesions treated with more than two stents; and 7) lesions with average stent area <5 mm² as measured by postintervention IVUS.

Beginning two days before scheduled angioplasty, patients were randomly assigned to two treatment groups: the troglitazone group of 28 patients with 35 stents, treated with 400 mg of troglitazone and dietary stabilization, and the control group of 27 patients with 33 stents, treated with dietary stabilization only. All patients were seen and examined monthly to monitor their general well-being and to identify potential adverse reactions, including liver dysfunction. At each visit, body weight, blood pressure, fasting PG, and serum chemical and hematological profiles, including liver enzyme levels, were determined. Our institutional ethics committee approved the protocol, and patients gave written, informed consent before randomization.

Baseline and final investigation. All patients underwent a 75-g oral glucose tolerance test (OGTT) 4 ± 1 days before coronary stent implantation and 2 ± 1 days before follow-up angiography. After fasting overnight, blood samples were obtained from each patient at baseline and at 1 h and 2 h after the glucose load. The PGs were measured by the enzymatic method using a Glucose Analyzer 1140 (Kyoto Daichi Kagaku, Kyoto, Japan), and immunoreactive insulin levels (IRIs) were measured by radioimmunoassay with the use of insulin Riabead II (Dainabot, Tokyo, Japan). The sum of plasma glucose (ΣPG = fasting PG + 1 h PG + 2 h PG) and the sum of insulin levels (ΣIRI = fasting IRI + 1 h IRI + 2 h IRI) were calculated.

Blood chemistry analyses, including glycosylated hemoglobin A1c levels and lipid levels, were performed at the same time. Glycosylated hemoglobin A1c was measured with the use of Hi-Auto A1c HA-8121 (Kyoto Daichi Kagaku). Total cholesterol and triglyceride levels were measured by the enzymatic method. High-density lipoprotein (HDL) cholesterol levels were measured in plasma after precipitation of low-density lipoprotein (LDL) and very-low-density lipoprotein. The LDL cholesterol concentrations were calculated using the following formula: LDL cholesterol = total cholesterol − HDL cholesterol − (triglyceride/5) (11).

Stent implantation. Palmaz-Schatz stents and MultiLink stents were implanted according to standard protocols. The IVUS was used to guide high-pressure adjunctive balloon inflation to achieve targeted stent expansion. The targeted expansion was a minimal stent area of ≥80% of the average of the proximal and distal reference lumen cross-sectional areas, by IVUS as well as complete stent-vessel wall apposition. All patients received 160 mg of aspirin and 200 mg of ticlopidine. The duration of ticlopidine treatment was four weeks.

Quantitative angiographic analysis. Quantitative coronary angiography was performed, using an automated edge detection system CMS (Medis Medical Imaging Systems), by a single individual who was unaware of the patients’ treatment assignments. A contrast-filled nontapered catheter tip was used for calibration. Minimal lumen diameter (MLD), reference diameter, percent diameter stenosis, and the diameter of the maximally inflated balloon were measured. Measurements from multiple projections were performed, and results from the “worst” views were recorded. A balloon-vessel ratio was calculated as the diameter of an inflated balloon divided by the coronary reference diameter.

Intravascular ultrasound imaging. The IVUS imagings were performed after intervention (following the final balloon inflation) and at follow-up (six months’ post-stent implantation). After administration of 1 to 2 mg of intracoronary isosorbide dinitrate, the 30-MHz, 3.2F IVUS catheter (Cardiovascular Imaging System) was advanced to the distal site in the coronary artery beyond the target lesion. Continuous images of the coronary artery, from beyond the target lesion to the aorto-ostial junction, were obtained as the ultrasound catheter was slowly withdrawn at 0.5 mm/s using a motorized pullback device. The IVUS images were recorded on a 0.5-inch VHS videotape for off-line analysis. The IVUS examinations were considered suitable for analysis if images were free from apparent ultrasound artifacts, such as oblique catheter positioning or nonuniform rotational distortion.

Quantitative IVUS measurements. With the use of computer-assisted planimetry (Tape-Measure, Indec System), quantitative IVUS measurements were performed by a single individual who was blinded to the patients’ treatment
Table 1. Clinical, Angiographic and Procedural Characteristics at Baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Troglitazone Group (n = 29 stents)</th>
<th>Control Group (n = 33 stents)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61 ± 11</td>
<td>60 ± 10</td>
<td>0.9887</td>
</tr>
<tr>
<td>Gender: male/female</td>
<td>23/6</td>
<td>27/6</td>
<td>&gt;0.9999</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.6 ± 2.5</td>
<td>25.1 ± 3.5</td>
<td>0.7941</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 ± 21</td>
<td>126 ± 22</td>
<td>0.1604</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>67 ± 10</td>
<td>69 ± 12</td>
<td>0.6066</td>
</tr>
<tr>
<td>Risk factors: no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>13 (45)</td>
<td>13 (39)</td>
<td>0.7974</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (69)</td>
<td>23 (70)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Current smoking</td>
<td>5 (17)</td>
<td>6 (18)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Treatments: no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>20 (69)</td>
<td>21 (64)</td>
<td>0.7895</td>
</tr>
<tr>
<td>Probucol</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>24 (83)</td>
<td>29 (88)</td>
<td>0.7221</td>
</tr>
<tr>
<td>Ca Antagonists</td>
<td>5 (17)</td>
<td>6 (18)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>24 (83)</td>
<td>29 (88)</td>
<td>0.7221</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>3 (10)</td>
<td>3 (9)</td>
<td>&gt;0.9999</td>
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<td>Angiographic and procedural factors</td>
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<td></td>
<td></td>
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<tr>
<td>Target vessel (LAD/RCA)</td>
<td>22/7</td>
<td>25/8</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.0 ± 0.4</td>
<td>3.0 ± 0.4</td>
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<tr>
<td>Minimal lumen diameter (mm)</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.2502</td>
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<tr>
<td>Diameter stenosis (%)</td>
<td>66.1 ± 5.8</td>
<td>67.7 ± 5.0</td>
<td>0.3420</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>10.5 ± 1.2</td>
<td>10.1 ± 1.3</td>
<td>0.2042</td>
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<tr>
<td>PS stents/ML stents</td>
<td>12/17</td>
<td>11/22</td>
<td>0.2144</td>
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<td>Balloon-artery ratio</td>
<td>1.07 ± 0.02</td>
<td>1.07 ± 0.03</td>
<td>0.6019</td>
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<tr>
<td>Final balloon pressure (atm)</td>
<td>12.5 ± 1.9</td>
<td>12.8 ± 2.1</td>
<td>0.7085</td>
</tr>
</tbody>
</table>

RESULTS

Troglitazone was well tolerated in 25 of the 28 patients in the troglitazone group. Two patients who experienced dizziness and one patient who had skin eruption after the beginning of troglitazone treatment were withdrawn from the study. No patient had persistent abnormalities in laboratory variables, including liver enzyme levels. Finally, 62 stented lesions in 52 patients underwent follow-up IVUS study. All patients underwent follow-up angiography as a part of the study protocol. At the time of follow-up, three patients had recurrent symptoms; however, none of the patients presented with unstable angina or myocardial infarction.

Selected demographic and clinical characteristics of the 52 patients are shown in Table 1. There were no statistically significant baseline differences between the two groups. Angiographic and procedural characteristics are also shown in Table 1. There were no significant differences in target vessels, angiographic reference diameter, MLD, lesion length, stent types, balloon-artery ratio, or final balloon pressure between the two groups.
Results of the OGGT are shown in Figure 1 and Table 2. There were no significant differences in PGs at baseline between the two groups. At six-month follow-up, however, PGs after the glucose load in the troglitazone group were significantly smaller than those in the control group. Decrease in HS-PG in the troglitazone group was significantly greater than that in the control group. There were no significant differences in insulin levels at baseline between the two groups. At six-month follow-up, however, insulin levels in the troglitazone group were significantly smaller than those in control group at follow-up.

Additionally, there were no significant differences in HbA1c levels between the two groups, either at baseline or at follow-up. There were no statistically significant differences in total cholesterol level, triglyceride level, HDL cholesterol level, or LDL cholesterol level at baseline between the two groups. Triglyceride level in the troglitazone group was significantly smaller than that in the control group at six-month follow-up, and the percent decrease in triglyceride levels in the troglitazone group was significantly greater than that in the control group. The LDL cholesterol levels in the troglitazone group were significantly greater than levels in the control group at six-month follow-up. However, there were no significant differences in the percent change in LDL-cholesterol levels between the two groups. There were no significant differences in total cholesterol levels or HDL cholesterol levels at follow-up between the two groups.

Results of quantitative coronary angiography are shown in Figure 2. There were no significant differences in MLD between the two groups, either at pre-intervention (1.0 ± 0.1 mm vs. 1.0 ± 0.1 mm, respectively, p = 0.2502) or post-intervention (2.9 ± 0.3 mm vs. 2.9 ± 0.4 mm, respectively, p = 0.9438). However, MLD at follow-up in the troglitazone group was significantly greater than that in the control group (2.2 ± 0.5 mm vs. 1.7 ± 0.5 mm, respectively, p = 0.0002).

The results of serial IVUS measurements are shown in Table 3. There were no significant differences in SA between the two groups either at post-intervention or six-month follow-up. However, LA at follow-up in the troglitazone group was significantly greater than that in the control group. Both the IA and intimal index at follow-up in the troglitazone group were significantly smaller than those in the control group.

**DISCUSSION**

Using serial IVUS assessments, the present study demonstrated that troglitazone reduced neointimal tissue proliferation after coronary stent implantation in patients with NIDDM. These results suggest that troglitazone can be effective in preventing restenosis after coronary stent implantation in patients with NIDDM.

Intravascular ultrasound permits direct measurements of cross-sectional areas of the stent, lumen, and neointimal tissue in vivo. Using the serial IVUS analysis, Hoffmann et al. (15) found that the stent did not recoil, and that in-stent restenosis was the result of neointimal tissue proliferation. Kornowski et al. (5) reported that the main reason for increased restenosis in patients with DM was exaggerated intimal hyperplasia in stented lesions. Diabetes mellitus is associated with hormonal and vascular abnormalities that promote vascular smooth muscle cell (VSMC) proliferation after vascular injury, including injury from catheter-based interventions (16). Increased VSMC proliferation may result from mitogens, such as platelet-derived growth factor (PDGF) and insulin-like growth factor, which stimulate cell growth (17–19). Insulin resistance and hyperinsulinemia have been implicated as possible common risk factors for NIDDM and atherosclerosis (20). Insulin administration has been suggested to promote VSMC growth (21), and although it is a weak mitogen alone, in physiologic concentrations it promotes the effects of PDGF and other growth factors of VSMC (22,23). Therefore, treatment strategies designed to limit cellular proliferation may be efficacious in reducing in-stent restenosis after coronary stent implantation in patients with NIDDM who have insulin resistance and hyperinsulinemia.

Troglitazone is a newly developed anti-diabetic agent from the thiazolidinedione class, which has been shown to
increase insulin sensitivity. The administration of troglitazone to patients with NIDDM improves both fasting and postprandial hyperglycemia and hyperinsulinemia (24–26). Besides its beneficial effects on the insulin-resistance state, troglitazone inhibits VSMC growth. Several experimental studies have reported that troglitazone inhibits growth-factor-induced proliferation and migration of cultured VSMC in vitro (6–9,27,28) and reduces intimal hyperplasia after balloon-induced vascular injury in vivo (6,8). In vitro studies have revealed that the anti-proliferative effect of troglitazone stems from its direct action on DNA synthesis rather than on any accompanying metabolic changes (6–9,27,28).

The present study demonstrated that administration of troglitazone benefits patients with NIDDM who have undergone coronary stent implantation, not only in reducing PG and insulin levels but also in reducing in-stent neointimal tissue proliferation. We did not address the question of what mechanism acts mainly to reduce neointimal tissue proliferation in the clinical setting. Further studies are necessary to determine which is the main mechanism of action in reducing neointimal tissue proliferation after coronary stent implantation in patients with NIDDM: 1) direct action on DNA synthesis or 2) improvement of the insulin-resistant state (improvement of hyperglycemia and/or hyperinsulinemia).

It has been reported that neointimal tissue proliferation after coronary stent implantation is also accelerated in patients with impaired glucose tolerance (IGT) (29) and that hyperinsulinemia in patients with IGT is associated with increased in-stent neointimal tissue proliferation (30). Because insulin resistance and hyperinsulinemia are often present in patients with IGT, the question emerges whether troglitazone benefits patients with IGT in reducing neointimal tissue proliferation after coronary stent implantation.
Nolan et al. (31) have reported that troglitazone decreases insulin resistance and improves glucose tolerance in patients with IGT and/or obesity. Further studies are warranted to determine whether troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with IGT. Because of the possibility of drug-induced hepatocellular injury (32), however, treatment with troglitazone may be limited.

**Study limitations.** The present study has some intrinsic limitations. The first is that it is a single-center, nonplacebo-controlled study with a small number of study patients. A large-scale, multicenter, placebo-controlled study is warranted to determine whether troglitazone reduces angiographic restenosis and/or target lesion revascularization after coronary stent implantation in patients with NIDDM. The second limitation is our exclusion of patients with previously treated DM and patients with fasting glucose levels >7.77 mmol/liter. In these patients, insulin response to a glucose load may be different because of their insulin secretory defect. It has been reported that troglitazone is effective both when given alone (24–26) and when given in combination with either sulfonylurea (33), metformin (34), or insulin (35). However, further study is necessary to determine whether troglitazone alone or combined with other oral hypoglycemic agents or insulin can reduce neointimal tissue proliferation after coronary stent implantation in NIDDM patients with insufficient insulin secretion.

The third limitation is that analyses of IVUS images at the central articulation of Palmaz-Schatz stents were excluded. Several angiographic studies and IVUS studies have pointed out that the central articulation is the most frequent site for restenosis in Palmaz-Schatz stents (36,37). However, recent study using serial IVUS showed that the tendency for increased neointimal tissue accumulation at the central articulation was modest in comparison to the otherwise uniform neointimal tissue accumulation over the length of the stent (15).

Finally, we used the intimal index to estimate neointimal tissue accumulation over the length of the stent. This intimal index can underestimate the focal in-stent restenosis in which the neointimal accumulation is localized. However, aggressive neointimal growth in the diffuse in-stent restenosis, which was indicated by a greater intimal index in this study, has been associated with a higher frequency of recurrent restenosis after angioplasty than that with focal in-stent restenosis.

**Other glitazones.** Recently, two other glitazones were clinically used. It has been reported that both rosiglitazone (38) and pioglitazone (39) improve glycemic control in patients with NIDDM. To our knowledge, however, there are no reports demonstrating that rosiglitazone reduces VSMC proliferation. It has been reported that pioglitazone inhibits growth-factor-induced proliferation of cultured VSMC in vitro (40) and reduces intimal hyperplasia after balloon-induced vascular injury in vivo (41). Further studies are necessary to determine whether other glitazones can reduce neointimal tissue proliferation after coronary stent implantation in patients with NIDDM.

**Conclusions.** Serial IVUS assessment has shown that administration of troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with NIDDM.

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