Thiazolidinedione Treatment Attenuates Diffuse Neointimal Hyperplasia in Restenotic Lesions After Coronary Stent Implantation in Type 2 Diabetic Patients: An Intravascular Ultrasound Study

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Abstract

Objectives. Thiazolidinedione treatment reduces neointimal tissue proliferation after coronary stent implantation in diabetic patients. However, in-stent restenosis still persists in patients treated with thiazolidinedione. The effect of thiazolidinedione treatment on the pattern of in-stent restenosis remains unclear. This study investigated whether thiazolidinedione treatment attenuates diffuse neointimal hyperplasia in restenotic lesions after coronary stent implantation in diabetic patients.

Methods. Volumetric intravascular ultrasound was performed at 6 months after coronary stent implantation in 76 patients with restenotic lesions who received either conventional anti-diabetic treatment (control group, n = 56) or thiazolidinedione treatment (thiazolidinedione group, n = 20).

Results. There were no significant differences between the two groups in stent volume (99 ± 32 vs 90 ± 20 mm³, respectively, p = 0.26) or in minimal lumen area in the stent (1.4 ± 0.6 vs 1.6 ± 0.5 mm², respectively, p = 0.11). However, there were significant reductions in neointimal volume (56 ± 25 vs 36 ± 11 mm³, respectively, p < 0.01) and neointimal index (56 ± 11% vs 41 ± 8%, respectively, p < 0.01) in the thiazolidinedione group. Coefficient of variation of neointimal tissue accumulation was greater in the thiazolidinedione group (45.5%) than in the control group (25.2%).

Conclusions. Intravascular ultrasound study demonstrated that together with reduction of overall neointimal tissue proliferation, thiazolidinedione treatment caused greater point-to-point heterogeneity in the neointimal tissue accumulation in restenotic lesions after coronary stent implantation. This finding strongly suggests that thiazolidinedione treatment attenuates diffuse in-stent restenosis in diabetic patients.

Key Words
- Diabetes mellitus (thiazolidinedione)
- Restenosis
- Stent
- Intravascular ultrasound

INTRODUCTION

Diabetes mellitus is a powerful determinant of in-stent neointimal hyperplasia and diffuse in-stent restenosis (ISR) after coronary stent implantation.1–4 Recent intravascular ultrasound (IVUS) studies have demonstrated that troglitazone and pioglitazone, anti-diabetic thiazolidinedione agents, reduce neointimal hyperplasia after coronary stent implantation in patients with type 2 diabetes mellitus.5–7
However, angiographic ISR still persisted in 19% to 23% of the stented lesions in patients treated with thiazolidinedione\(^5,7\). The pattern of ISR may convey prognostic information about subsequent target vessel revascularization. Previous studies showed a high recurrence rate after treating diffuse ISR\(^1,8\).

The present study investigated whether thiazolidinedione treatment attenuates diffuse neointimal hyperplasia in restenotic lesions after coronary stent implantation in diabetic patients.

**SUBJECTS AND METHODS**

**Study patients and protocol**

This prospective, randomized trial in Kobe General Hospital evaluated the effects of troglitazone and pioglitazone on neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus\(^5,7\). Quantitative angiographic assessments were done at baseline, post-stenting and at 6-month follow-up using CMS (Medis Medical Imaging Systems). Measurements from multiple projections were performed and the least favorable findings were recorded. ISR was defined as \(\geq 50\)\% diameter stenosis within the stent at follow-up. The Kobe General Hospital IVUS-diabetes mellitus registry contains 184 stented lesions, of which 76 lesions with angiographic ISR at a 6-month follow-up were selected for the current analysis. There were 20 lesions in the thiazolidinedione group and 56 lesions in the control group. All patients gave written informed consent before randomization as previously reported\(^5,7\). The study protocol was approved by the institutional ethic committee.

**Intravascular ultrasound imaging and analysis**

IVUS was performed at a 6-month follow-up. Images were acquired using commercially available imaging systems with 30 MHz mechanical transducers (CVIS/Boston Scientific Corporation) with automated transducer pullback (0.5 mm/sec) after administration of intracoronary isosorbide dinitrate (1 to 2 mg). IVUS at 6-month follow-up was obtained before repeat coronary intervention for the ISR.

Quantitative analysis was performed with validated, commercially available planimetry software (Tapemeasure, IndecSystem, Inc.). Cross-sectional measurements of stent and lumen area were performed manually every 1 mm throughout the stent. Simpson method was used to calculate stent, lumen, and neointimal volumes. Neointimal volume index was calculated as neointimal volume divided by stent volume. Neointimal area index was calculated as neointimal area divided by stent area at the image slice with minimal lumen area. The axial variability of neointimal proliferation by dividing the standard deviation (SD) of the neointimal area by the mean neointimal area\(^11\).

**Statistical analysis**

Continuous data are presented as mean \(\pm\) SD, and categorical data are presented as frequencies. Continuous variables were compared using the Mann-Whitney U-test. Categorical variables were compared using the Fisher exact probability test. Results of IVUS measurements, clinical, angiographic and procedural characteristics were determined using lesion-based assessments. A two-side value of \(p < 0.05\) was considered significant.

**RESULTS**

As shown in Table 1, there were no significant differences in patient characteristics between the two groups. Glucose levels at baseline and at 6-month follow-up were equivalent in both groups. As shown in Table 2, there were no significant differences between the two groups in medical treatment except the use of alpha-glucosidase inhibitors was more frequent in the control group. Table 3 summarizes angiographic and procedural characteristics. There were no significant differences in angiographic and procedural characteristics between the two groups. Fig. 1 shows the results of quantitative coronary angiographic analysis. There were no significant differences between the two groups in minimal lumen diameter at baseline, post-stenting, or 6-month follow-up.

As shown in Fig. 2, volumetric IVUS analysis demonstrated that there was no significant difference in stent volume between the two groups (99 \(\pm\) 32 vs 90 \(\pm\) 20 mm\(^2\), \(p = 0.26\)). However, lumen volume in the thiazolidinedione group was significantly greater than in the control group. Neointimal volume and index in the thiazolidinedione group were significantly smaller than in the control group (56 \(\pm\) 25 vs 36 \(\pm\) 11 mm\(^2\), \(p < 0.01\); 56 \(\pm\) 11\% vs 41 \(\pm\) 8\%, \(p < 0.01\)). As shown in Fig. 3, IVUS
measurement of the image slice with minimal lumen area showed no significant difference in stent area, lumen area (1.4 ± 0.6 vs 1.6 ± 0.5 mm², \( p = 0.11 \)), neointimal area, or neointimal area index between the two groups. We assessed the axial variability in neointimal proliferation in the two groups by calculating the CV of the neointimal area (CV = SD of neointimal area/mean neointimal area). The CV of neointimal area was significantly greater in the thiazolidinedione group than in the control group (45.5% vs 25.2%, \( p < 0.01 \)). Fig. 4.

**Fig. 5** shows representative cases of the two groups, to demonstrate the axial distribution of the neointimal area standardized by the mean neointimal area. Greater point-to-point variability of neointimal area was seen in the thiazolidinedione group.

**Discussion**

The present IVUS study demonstrated that together with the reduction of overall neointimal hyperplasia, thiazolidinedione treatment caused greater point-to-point heterogeneity in neointimal accumulation in restenotic lesions after coronary stent implantation.

The mechanism of ISR is the result of neointimal hyperplasia. Histological studies in humans have demonstrated that early thrombus formation and acute inflammation are followed by neointimal tissue proliferation in the chronic stage after coro.
Table 3  Angiographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Thiazolidinedione (n = 20)</th>
<th>Control (n = 56)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD/LCX/RCA</td>
<td>13/3/4</td>
<td>37/6/13</td>
<td>0.69</td>
</tr>
<tr>
<td>Lesion classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/B/C</td>
<td>2/14/4</td>
<td>4/41/8</td>
<td>0.65</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.7 $\pm$ 0.2</td>
<td>2.8 $\pm$ 0.4</td>
<td>0.27</td>
</tr>
<tr>
<td>MLD-baseline (mm)</td>
<td>0.8 $\pm$ 0.3</td>
<td>0.8 $\pm$ 0.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>11.9 $\pm$ 3.2</td>
<td>12.3 $\pm$ 3.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MultiLink/NIR/Terumo</td>
<td>12/8/0</td>
<td>42/13/1</td>
<td>0.16</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>15.9 $\pm$ 3.3</td>
<td>16.8 $\pm$ 4.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Balloon diameter (mm)</td>
<td>2.8 $\pm$ 0.3</td>
<td>2.9 $\pm$ 0.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Balloon pressure (atm)</td>
<td>11.5 $\pm$ 1.7</td>
<td>11.8 $\pm$ 2.1</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Continuous values are mean $\pm$ SD.
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; MLD = minimal lumen diameter.

Fig. 1  Quantitative coronary angiographic analysis demonstrating no significant differences between the two groups in minimal lumen diameter at baseline, post-stent, or 6-month follow-up.

Fig. 2  Volumetric intravascular ultrasound analysis demonstrating no significant difference between the two groups in stent volume.
Lumen volume in the thiazolidinedione group was significantly greater than in the control group, and neointimal volume and index in the thiazolidinedione group were significantly smaller than in the control group.
nary stent implantation. Analysis of directional atherectomy specimens of early ISR tissue showed predominantly smooth muscle cells. The lesion cellularity decreases with time over weeks or months, and extracellular matrix (proteoglycans and collagen) becomes the predominant component of restenotic lesions. ISR is predominantly affected by local conditions at the site of coronary stenting, such as vessel size, stent type, and stent length.

Several IVUS studies have reported that greater pre- or post-interventional plaque burden is associated with greater neointimal tissue proliferation after stent implantation. Postmortem histologic analysis of ISR demonstrated that neointimal thick-
mess at stent strut sites was greatest at sites of medi-

al injury\textsuperscript{15}. These local conditions may contribute to the focal ISR or point-to-point heterogeneity of neointimal tissue accumulation even in diabetic patients with thiazolidinedione treated. The presence of diabetes mellitus accelerates the process of neointimal tissue proliferation and promotes the development of diffuse ISR. Diabetes mellitus results in increased inflammation, increased platelet activation, impaired fibrinolysis, and abnormal coagulation. Patients with type 2 diabetes mellitus have increased inflammation as indicated by increased generation of reactive oxygen species by mononuclear cells\textsuperscript{21}. Patients with diabetes mellitus also have elevated levels of interleukin-6, tumor necrosis factor-alpha, and C-reactive protein\textsuperscript{22,23}. Type 2 diabetes mellitus enhances the synthesis of plasminogen activator inhibitor type 1 (PAI-1)\textsuperscript{24}. PAI-1 inhibits endogenous intravascular fibrinolysis, and increased PAI-1 levels lead to impaired fibrinolysis and thus the prothrombotic state\textsuperscript{25}. PAI-1 is also implicated in the inhibition of proteolysis, which allows for increased deposition of extra-cellular matrix, an important component of restenotic lesions in diabetic patients\textsuperscript{26}. Increased smooth muscle cell proliferation with exaggerated neointimal hyperplasia has also been demonstrated in diabetic animal models\textsuperscript{26,27}.

The thiazolidinedione agents are a family of per-

oxisome proliferator activated receptor-gamma lig-

ands, and form a new class of pharmacological agents for the treatment of type 2 diabetes mellitus\textsuperscript{28-30}. Thiazolidinedione has potential protective effects on cardiovascular function. These drugs inhibit growth factor-induced proliferation of vascular smooth muscle cells, inhibit smooth muscle cell migration, and attenuate the development of neointimal hyperplasia after balloon-induced vascular injury in animal models\textsuperscript{31-36}. Recent studies have demonstrated that pioglitazone enhances apoptosis in balloon-induced vascular injury, and reduces coronary vascular inflammation in an animal model\textsuperscript{37,38}. Thiazolidinedione reduces PAI-1 and C-reactive protein concentration in diabetic patients\textsuperscript{39-42}. Rosiglitazone reduces ISR after coronary stent implantation in diabetic patients. Rosiglitazone also reduces high-sensitivity C-reactive protein concentration in diabetic patients\textsuperscript{43}. These studies suggest that thiazolidinedione treatment attenuates the accelerated process of neointimal hyperplasia and causes greater point-to-point heterogeneity in neointimal accumulation in ISR via several mechanisms: anti-inflammatory effects, down-regulation of PAI-1 expression, inhibition of cellular tissue growth, and enhancing regression of developed neointimal tissue after coronary stent implantation. Further study is required to evaluate whether the effect of thiazolidinedione on high-sensitivity C-reactive protein levels or PAI-1 expression is associated with reduction of neointimal tissue proliferation after coronary stent implantation in diabetic patients.

Clinical implications

The present study suggests that thiazolidinedione treatment attenuates diffuse ISR in diabetic patients. The pattern of ISR gives prognostic information about subsequent target vessel revascularization. Diffuse ISR is associated with high recurrence rate after repeat coronary intervention\textsuperscript{1-4}. Therefore, thiazolidinedione treatment may provide subsequent benefits for diabetic patients who undergo repeat coronary intervention. Further studies are warranted to determine whether thiazo-

lidinedione treatment reduces subsequent restenosis after repeat coronary intervention for the ISR.

Study limitations

The present study had some intrinsic limitations. This study was a single center, non-placebo-con-

trolled study with a small number of patients, raising the possibility of selection bias and low statisti-

cal power. IVUS cannot be used to measure lumen dimensions smaller than the imaging catheter. When the tissue encompassed the IVUS catheter, the lumen was assumed to be the physical size of the IVUS catheter. Therefore, 1.0 mm was the smallest minimal lumen diameter, and 0.8 mm\textsuperscript{2} was the smallest cross-sectional lumen area that could be measured before re-intervention. This limitation may underestimate the late lumen loss or neointimal tissue proliferation in severely restenotic lesions. In addition, because of the finite resolution of IVUS, very thin neointimal proliferation on the stent struts could not be differentiated by quantitative IVUS analysis. A previous angiographic study classified diffuse ISR into three classes, diffuse intra-stent ISR, diffuse proliferative ISR, and diffuse ISR with total occlusion\textsuperscript{22}. The rate of subsequent revascularization after repeat intervention treatment in diffuse proliferative ISR and diffuse ISR with total occlusion was greater than in diffuse

\textsuperscript{4} Takan, Yamamuro, Tamita et al
intra-stent ISR. Because totally occluded diffuse ISR was difficult to cross with the IVUS catheter before repeat intervention, diffuse ISR with total occlusion was not included in the current IVUS analysis. In addition, because IVUS images were obtained within the stent, quantitative IVUS analysis. In addition, because IVUS images were obtained within the stent, quantitative IVUS analysis might underestimate diffuse proliferative ISR.

CONCLUSIONS

Together with the reduction of overall neointimal hyperplasia, thiazolidinedione treatment causes greater point-to-point heterogeneity in neointimal accumulation. This finding strongly suggests that thiazolidinedione treatment attenuates diffuse ISR after coronary stent implantation in diabetic patients.

References


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