ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2010.08.006

Different Patterns of Vascular Response Between Patients With or Without Diabetes Mellitus After Drug-Eluting Stent Implantation

Optical Coherence Tomographic Analysis

Nobuyoshi Tanaka, MD, Mitsuyasu Terashima, MD, Sudhir Rathore, MD, Tsuyoshi Itoh, MD, Maoto Habara, MD, Kenya Nasu, MD, Masashi Kimura, MD, Tatsuya Itoh, MD, Yoshihisa Kinoshita, MD, Mariko Ehara, MD, Etsuo Tsuchikane, MD, Keiko Asakura, MD, Yasushi Asakura, MD, Osamu Katoh, MD, Takahiko Suzuki, MD

Toyohashi, Japan

Objectives We performed this study to investigate with optical coherence tomography (OCT) the vascular response after sirolimus-eluting stent (SES) implantation between patients with and those without diabetes mellitus (DM).

Background The difference in vascular response after SES implantation between patients with and those without DM has not been fully evaluated with OCT.

Methods Optical coherence tomography was performed to examine 74 nonrestenotic SES implanted in 63 patients (32 with DM and 31 without DM) at 9 months after SES implantation. For struts showing neointimal coverage, the neointimal thickness on the luminal side of each strut section was measured, and neointimal characteristics were classified into high, low, and layered signal pattern.

Results Baseline patient characteristics and lesion and procedural characteristics data were similar between the 2 groups. In total, 11,422 struts were analyzed. High signal neointima was observed in 90.2 ± 13.9%, low signal neointima in 7.3 ± 10.0%, and layered neointima in 2.7 ± 5.8%/stents. There was higher incidence of low signal neointima (10.5 ± 10.3% vs. 4.5 ± 5.6%, $p = 0.003$), neointimal thickness was larger (median: 106.8 μm, interquartile range: 79.3 to 130.4 μm vs. median: 83.5 μm, interquartile range: 62.3 to 89.3 μm; $p < 0.0001$), and neointimal coverage of stent struts was higher (92.1 ± 6.2% vs. 87.2 ± 11.9%; $p = 0.03$) in DM patients.

Conclusions High signal neointimal pattern was predominantly observed, and low or layered signal pattern was observed in some cases. In DM patients, low signal neointima was observed with high frequency. Neointimal coverage and neointimal thickness was also higher in DM patients as compared with non-DM patients. (J Am Coll Cardiol Intv 2010;3:1074–9) © 2010 by the American College of Cardiology Foundation

From the Department of Cardiology, Toyohashi Heart Center, Toyohashi, Japan. The authors have reported that they have no relationships to disclose. Drs. Tanaka and Rathore have contributed equally to this paper.

Manuscript received March 24, 2010; revised manuscript received June 17, 2010, accepted August 5, 2010.

The introduction of the drug-eluting stent (DES) has resulted in suppressing neointimal hyperplasia and thereby reducing restenosis rates as compared with bare-metal stent (BMS) (1,2). However, the issue of late stent thrombosis has emerged as a safety concern (3) with the use of DES. Diabetes mellitus (DM) has been shown to be a strong independent predictor of restenosis (4,5) and late stent thrombosis (6,7) after sirolimus-eluting stent (SES) implantation. Therefore, it has been postulated that vascular healing and response in patients with DM after SES implantation might be different from patients without DM. Optical coherence tomography (OCT) has been recently used for daily clinical practice. Because resolution of OCT is 10× (10 to 20 μm) higher than intravascular ultrasound (IVUS), the stent strut coverage with neointima after implantation could be better visualized and quantified by OCT. To date, the difference in vascular healing and vascular response after SES implantation in patients with and those without DM has not been reported. The objective of this study is to evaluate the differences and patterns of vascular healing and vascular response at 9 months after SES implantation in patients with (DM group) and those without DM (non-DM group) as assessed by OCT.

Methods

Patient population. We evaluated 74 nonrestenotic SES (Cypher, Cordis, Miami Lakes, Florida) implanted in 63 patients (32 DM group, 31 non-DM group), who agreed to undergo follow-up coronary angiography and OCT study. The OCT analysis and coronary angiography was performed at 9 months after SES implantation. All patients received dual antiplatelet therapy with aspirin 100 mg/day and ticlopidine 200 mg/day or clopidogrel 75 mg/day before and after SES implantation. The DM group was defined as patients treated with oral diabetes agent or insulin at the time of percutaneous coronary intervention.

We excluded patients with ST-segment elevated myocardial infarction, contraindication to dual antiplatelet therapy, restenotic lesions after balloon angioplasty, left ventricular ejection fraction <30%, chronic renal dysfunction as indicated by serum creatinine more than 1.5 mg/dl, left main coronary artery lesions, ostial lesions and severe tortuous lesion, failure to obtain clear image by IVUS or OCT, or lesions inappropriate for IVUS or OCT examination. The study was approved by our institutional review board, and written informed consent was obtained from all study patients before catheterization.

Quantitative coronary angiographic analysis. All baseline, procedural, and follow-up angiography was performed immediately after administration of 200 μg of intracoronary nitroglycerin, and the treated lesion was evaluated with 2 or more angiographic projections. Quantitative coronary angiography (QCA) was performed by 2 experienced angiographers with the Cardiovascular Measurement System (CMS-MEDIS, Medical Imaging Systems, Leiden, the Netherlands). Lesion length, reference diameter, minimal lumen diameter (MLD), and percentage diameter stenosis were measured with the view showing the smallest lumen diameter at diastolic frames. The QCA analysis was performed at baseline, after procedure, and 9-month follow-up. Acute gain was defined as the difference between baseline and post-procedural MLD, and late loss was defined as the difference between post-procedural and follow-up MLD.

OCT image acquisition. The OCT image acquisition was performed with a commercially available system for intracoronary imaging (LightLab Imaging, Inc., Westford, Massachusetts). The ImageWire (LightLab Imaging, Inc.) was positioned distal to the stented segment with over-the-wire type occlusion balloon catheter (Helios, LightLab Imaging Inc.). To clear blood from the imaging site, the occlusion balloon was inflated to 0.5 to 0.7 atm with a customized inflation device, and Lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon at the rate of 0.5 to 0.9 ml/s. Motorized pullback OCT imaging was performed at a rate of 1.0 mm/s. All images of the stents were acquired at 15 frames/s and were digitally stored for offline analysis.

OCT image analysis. Offline analysis was performed with the proprietary LightLab software (LightLab Imaging). Cross-sectional OCT images were analyzed at 1-mm intervals by 2 independent observers, who were blinded to clinical and procedural characteristics. The stented segment was defined as the region between the first and the last frame with circumferentially visible struts on the OCT image. The stent strut apposition to the vessel wall and neointimal coverage were assessed for each stent strut. Fully covered stent strut was defined as complete coverage of the stent strut on the luminal side by visible neointima. This means that neointimal thickness has to be at least 10 μm to be detected by the OCT. The malapposition of a strut was defined as a distance of >170 μm between the middle of stent strut reflection and the vessel wall (8). Strut coverage ratio and mean neointimal thickness were examined on a per-stent basis. Binary strut coverage (%) was calculated as: (number of strut sections covered/total number of strut sections examined) × 100 (9). For struts showing neointimal coverage, the neointimal thickness on the luminal side of each strut section was measured, and the neointimal characteristics were classified into high signal pattern: neo-

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
DM = diabetes mellitus
IVUS = intravascular ultrasound
MLD = minimal lumen diameter
OCT = optical coherence tomography
QCA = quantitative coronary angiography
SES = sirolimus-eluting stent(s)

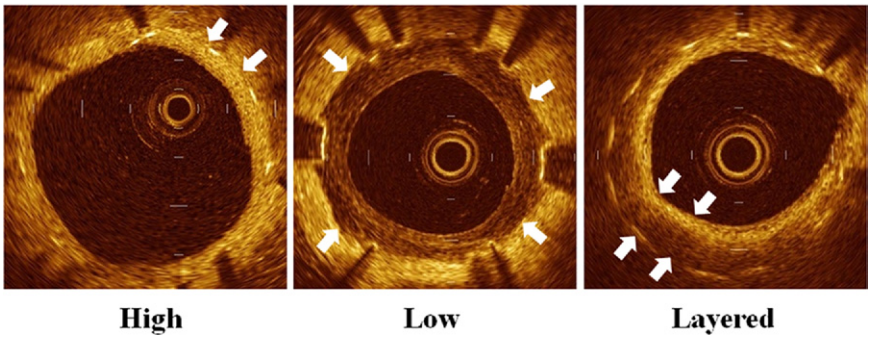

Figure 1. Neointimal Classification at 9-Month Follow-Up After Sirolimus-Eluting Stent Implantation

Neointimal characteristics were classified into high signal pattern, low signal pattern, and layered signal pattern, as indicated by **white arrows**.

intima is of high density and line could not be drawn between neointimal layer and intima, because of high signal intensity throughout; low signal pattern: neointima is of low density, and we can clearly draw the line between neointimal layer and intima; and layered signal pattern: neointima is of mixed density, and deeper layers are low density, and the luminal side is high density (Fig. 1).

Statistical analysis. Statistical analysis was performed with StatView version 5 (SAS Institute, Inc. Cary, North Carolina). Data were expressed as mean ± SD or as median (25th, 75th percentile) for continuous variables and as frequencies for categorical variables. The chi-square test or Fisher exact test was used for comparing frequencies of occurrence. Continuous variables between different categories were compared by either Mann-Whitney *U* test or unpaired *t* test. Stent-wise comparisons were made by a single experienced observer without correction. A p value <0.05 was considered to be statistically significant.

Results

Baseline clinical, lesion, and procedural characteristics. The baseline patient demographic, lesion, and procedural characteristics for both groups are shown in Tables 1 and 2. Baseline patient, lesion, and procedural characteristics were similar in the 2 groups. Follow-up angiography and OCT analysis was performed at 9.2 ± 1.8 months in the DM group and 9.1 ± 1.5 months in the non-DM group ($p = 0.8$). In addition, there was no significant difference in the dual antiplatelet therapy compliance between the 2 groups (aspirin and ticlopidine or clopidogrel; 96.9% in the DM group, 93.5% in the non-DM group; $p = 0.54$) during follow up. All OCT images at follow-up were acquired successfully without any complications.

QCA data analysis. The QCA data are shown in Table 3. Baseline angiographic variables were similar for both groups. Furthermore, there was no significant difference in the post-procedural MLD, percentage diameter stenosis, and acute gain between the 2 groups. At 9-month follow-up, MLD was larger, and percentage diameter stenosis was lower in the non-DM group, as compared with the DM group (2.70 ± 0.39 mm vs. 2.21 ± 0.55 mm, $p < 0.01$, and 11.0 ± 9.2% vs. 17.1 ± 12.8%, $p = 0.03$, respectively). Furthermore, late loss was larger in the DM group than in the non-DM group (0.32 ± 0.39 mm vs. 0.02 ± 0.34 mm, $p < 0.01$).

OCT analysis. The OCT analysis was performed at 9-month follow-up to examine the implanted 74 SES in 63 patients (32 with diabetes, and 31 without diabetes) (Table 4). There were no incidences of ventricular fibrillation, vessel injury, or visible thrombus formation during the OCT procedure. In total 11,242 strut sections were analyzed. Stent strut

Table 1. Baseline Patient Characteristics

Variables	DM Group (n = 32)	Non-DM Group (n = 31)	p Value
Age, yrs	65.1 ± 10.4	68.5 ± 11.5	0.22
Male sex	27 (84.4)	23 (74.2)	0.32
Hypertension	25 (78.1)	25 (80.6)	0.80
Hyperlipidemia	20 (62.5)	24 (77.4)	0.20
Current smoking	12 (37.5)	10 (32.3)	0.66
Renal dysfunction (Cr >1.2)	1 (3.1)	1 (3.2)	0.98
Prior myocardial infarction	9 (28.1)	7 (22.6)	0.61
Prior PCI	14 (43.8)	15 (48.4)	0.71
Prior CABG	1 (3.1)	1 (3.2)	0.98
Multi-vessel involvement	27 (84.4)	26 (83.9)	0.96
Unstable angina pectoris	5 (15.6)	5 (16.1)	0.96
Chronic stable angina	27 (84.4)	26 (83.9)	0.96
LVEF, %	52.4 ± 9.3	53.8 ± 8.4	0.55
Statin	21 (65.6)	20 (64.5)	0.93
ACEI, ARB	20 (62.5)	18 (58.1)	0.72
Dual antiplatelet therapy	31 (96.9)	29 (93.5)	0.54

Values are given as mean ± SD or n (%).

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass surgery; Cr = creatinine; DM = diabetes mellitus; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Lesion and Procedural Characteristics

Variables	DM Group (n = 32)	Non-DM Group (n = 31)	p Value
Vessel treated			
LAD	13 (40.6)	14 (45.2)	
LCx	10 (31.3)	9 (29.0)	0.72
RCA	9 (28.1)	8 (25.8)	
AHA/ACC typeB2/C lesion	27 (84.4)	25 (80.6)	0.70
Stent diameter, mm	2.89 ± 0.37	3.03 ± 0.32	0.11
Stent length, mm	22.7 ± 5.8	20.8 ± 5.1	0.66
Multiple overlapping stents	6 (18.8)	5 (16.1)	0.78
Maximum inflation pressure, atm	17.8 ± 3.7	18.3 ± 4.1	0.59

Values are given as n (%) or mean ± SD.
AHA/ACC = American Heart Association/American College of Cardiology; DM = diabetes mellitus; LAD = left anterior descending artery; LCx = left circumflex; RCA = right coronary artery.

coverage and neointimal thickness at 9 months were significantly higher in the DM group compared with the non-DM group (92.1 ± 6.2% vs. 87.2 ± 11.9%; p = 0.03) (Fig. 2), (median: 106.8 μm, interquartile range: 79.3 to 130.4 μm vs. median: 83.5 μm, interquartile range: 62.3 to 89.3 μm; p < 0.0001), respectively (Fig. 3).

In terms of distribution of different patterns of neointimal characteristics, high signal pattern of neointima was dominantly seen in this analysis: high signal pattern (90.2 ± 13.9%), low signal pattern (7.3 ± 10.0%), and layered signal pattern (2.7 ± 5.8%) (Fig. 4).

The different pattern of neointimal characteristics was also assessed between DM and non-DM groups (Fig. 5). The frequency of high signal pattern was observed significantly higher in the non-DM group (86.2 ± 14.3% vs. 94.0 ± 7.6%; p = 0.004), whereas low signal pattern was observed significantly more frequently in the DM group (10.5 ± 10.3% vs. 4.5 ± 5.6%; p = 0.003). The frequency of layered signal pattern was observed similarly between the 2 groups (3.2 ± 5.6% vs. 1.4 ± 3.4%).

Table 3. Quantitative Angiographic Data Before, After, and Follow-Up Period

Variables	DM Group (n = 32)	Non-DM Group (n = 31)	p Value
Lesion length, mm	21.8 ± 11.1	18.2 ± 8.0	0.14
Reference diameter, mm	2.57 ± 0.60	2.78 ± 0.39	0.08
Minimal lumen diameter, mm			
Before procedure	0.90 ± 0.34	1.06 ± 0.36	0.06
After procedure	2.63 ± 0.56	2.83 ± 0.38	0.18
Follow-up	2.21 ± 0.55	2.70 ± 0.39	<0.01
% diameter stenosis			
Before procedure	64.6 ± 12.0	62.0 ± 11.8	0.37
After procedure	9.80 ± 8.30	12.4 ± 11.3	0.29
Follow-up	17.1 ± 12.8	11.0 ± 9.2	0.03
Acute gain, mm	1.63 ± 0.47	1.69 ± 0.41	0.93
Late loss, mm	0.32 ± 0.39	0.02 ± 0.34	<0.01

Values are given as mean ± SD.
DM = diabetes mellitus.

Table 4. OCT Analysis at Follow-Up Period

Variables	DM Group (n = 32)	Non-DM Group (n = 31)	p Value
No. of stents, n	38	36	—
No. of stent struts counted, n	5,921	5,321	—
Covered struts	92.1 ± 6.2	87.2 ± 11.9	0.03
Neointimal thickness, μm	106.8 (79.3–130.4)	83.5 (62.3–89.3)	<0.0001
High signal neointima	86.2 ± 14.3	94.0 ± 7.6	0.004
Low signal neointima	10.5 ± 10.3	4.5 ± 5.6	0.003
Layered signal neointima	3.2 ± 5.6	1.4 ± 3.4	0.1

Values are given as %, mean ± SD, or median (interquartile range).
DM = diabetes mellitus; OCT = optical coherence tomography.

Discussion

The main findings of our study are: 1) there was a significantly higher number of stent struts covered with neointima, and there was higher neointimal thickness in patients with diabetes mellitus as compared with non-DM patients after SES implantation at 9 months; 2) there was higher incidence of low signal pattern neointima seen in patients with diabetes mellitus.

Some other studies (10) have shown that 90% of the stent struts were covered by neointima after 6 months of SES implantation, as observed by OCT. These results are similar to our study. Previous studies using IVUS analysis in BMS have shown that in-stent neointimal hyperplasia was larger in patients with DM as compared with non-DM patients. It has been suggested that DM itself causes exaggerated intimal hyperplasia and is the major risk factor for higher in-stent restenosis rate (11).

Treatment with DES significantly suppresses neointimal proliferation in patients with DM in comparison with BMS

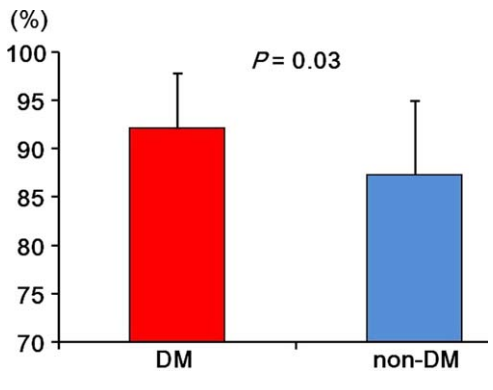

Figure 2. Comparison of Neointimal Coverage Rate Between DM Group and Non-DM Group

DM = diabetes mellitus.

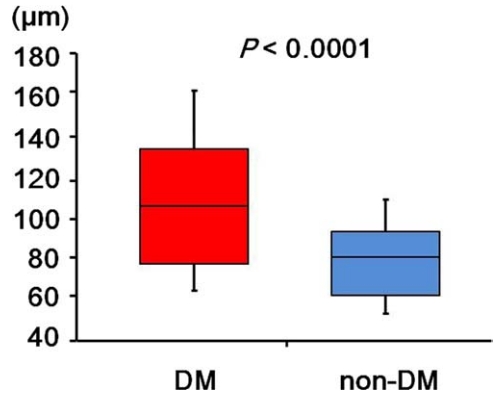

Figure 3. Box Plots Showing Comparison of Neointimal Thickness Between DM and Non-DM Groups

Values for neointimal thickness (μm) are presented as median with an interquartile range and minimum and maximum values at the extreme. DM = diabetes mellitus.

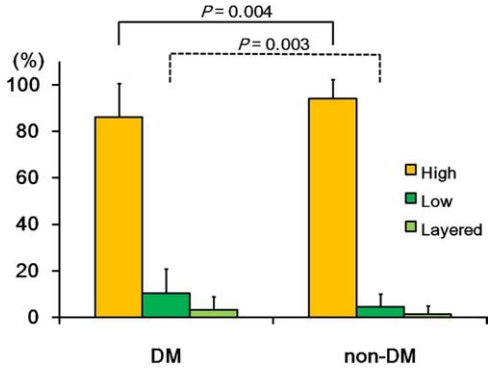

Figure 5. Difference of Neointimal Characteristics Between DM and Non-DM Groups

High signal pattern was significantly higher in non-DM group (mean ± SD, 86.2 ± 14.3% vs. 94.0 ± 7.6%; p = 0.004); low signal pattern was significantly more frequent in DM group (mean ± SD, 10.5 ± 10.3% vs. 4.5 ± 5.6%; p = 0.003). DM = diabetes mellitus.

(12,13). Moussa et al. (12) and Jiménez-Quevedo et al. (13) have commented that, despite the significant reductions in late loss and restenosis in diabetic patients receiving the sirolimus-eluting stent, the absolute late loss and restenosis remain higher than that observed in non-DM patients. We have also shown higher late loss in the DM group, and our OCT analysis showed more frequent stent strut coverage, thicker neointima, and higher neointimal hyperplasia in patients with DM as compared with non-DM after SES implantation.

These results are supported by the fact that the effectiveness of Rapamycin for inhibiting migration of smooth muscle cells is less subject to hyperglycemic conditions as compared with normoglycemia (14). Diabetes is known to be associated with hormonal and vascular abnormalities that promote smooth muscle cell proliferation after vascular injury, including injury after coronary interventions (15). Increased smooth muscle proliferation in diabetic patients might result from mitogens (such as platelet-derived growth factor and insulin-like growth factor) that stimulate cell growth and deleterious vascular effects of endothelial dysfunction and excessive extracellular matrix production (16,17).

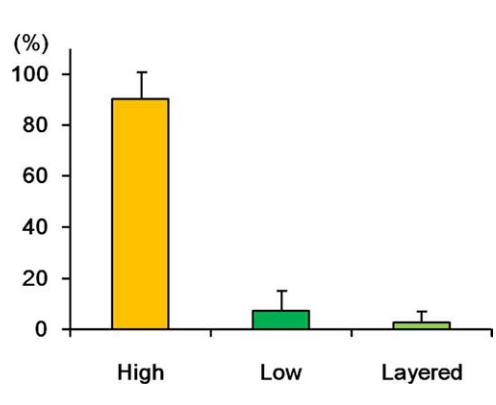

Figure 4. Distribution of Neointimal Characteristics for Stent Struts Showing Neointimal Coverage

The incidence of stent thrombosis has been related to the higher incidence of exposed stent struts and poor endothelialization in the previous study (13). However, they have not observed different composition of neointima as a cause of stent thrombosis. Ideally, the higher amount of neointima and endothelialization of the stent struts should be protective of stent thrombosis in diabetic patients. On the contrary, diabetes mellitus has been identified as an independent predictor of stent thrombosis after SES implantation (6,7). The exact underlying mechanism is unknown, and it has been postulated that diabetic patients have multivessel coronary artery disease and higher risk profile, predisposing them for stent thrombosis.

The characteristics and the quality of neointima formation could potentially contribute to this higher rate of stent thrombosis in diabetic patients. Interestingly, we have observed a significantly higher frequency of neointima with low signal pattern in patients with diabetes mellitus as compared with patient without diabetes mellitus. Neointima pattern after BMS implantation has mainly shown high signal pattern (18), whereas the low-signal pattern seen in the present study was different from the usual pattern of neointima. Despite excessive intimal proliferation and favorable stent strut coverage, stent thrombosis rates tend to be higher in patients with DM in the clinical setting. This contradictory phenomenon can be explained by "the difference in characteristics and quality of neointimal formation." The pathological assessment by Joner et al. (19) has suggested that the significant, incomplete endothelialization

and persistent fibrin deposition were observed after DES (sirolimus-, paclitaxel-eluting stent) implantation as compared with BMS implantation.

Neointima observed as low signal pattern by OCT in the present study could be composed of immature neointima, extra cellular matrix, organized thrombi, and proteoglycan caused by delayed re-endothelialization, as seen in pathological studies (16,17). These changes could play a role in the pathogenesis of thrombus formation. Moreover, patients with DM as compared with non-DM patients have exaggerated vascular endothelial damage after stent implantation. As a consequence, neointima that is observed as low signal pattern could be caused by delayed re-endothelialization. However, there is no histopathological data to support this hypothesis.

Larger studies involving serial assessment of the neointima by OCT are needed to further elucidate this process. Moreover, comparison and correlation between OCT characteristics and histopathological specimens obtained during atherectomy could help in understanding the composition of neointima. Clinical association between type of neointimal formation by OCT and stent thrombosis needs to be confirmed.

Study limitations. First, this study is a retrospective, observational study of prospectively collected data. Second, the sample size was relatively small. Third, there is a lack of clinical follow-up data. A large randomized multicenter clinical study is warranted to more accurately evaluate the vascular response after DES implantation in patients with diabetes mellitus.

Conclusions

This is the first study analyzing the OCT characteristics of neointima after SES implantation in patients with diabetes. We have observed that efficacy of suppressing neointimal proliferation is attenuated in patients with DM as compared with patients without DM. Furthermore, a low-signal pattern of neointima was observed with higher frequency in DM patients, suggesting different vascular response and neointima proliferation in DM patients as compared with non-DM patients.

Reprint requests and correspondence: Dr. Mitsuyasu Terashima, Toyohashi Heart Center, 21-1 Gobudori, Oyama-cho, Toyohashi 441-8530, Japan. E-mail: terashima@heart-center.or.jp.

REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al., for the RAVEL Study Group. A randomized comparison of sirolimus-eluting stent with a standard stent for coronary revascularization. N Engle J Med 2002; 346:1773–80.
2. Moses JW, Leon MB, Popma JJ, et al., for the SIRIUS Investigators. Sirolimus eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
3. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus eluting stent implantation. Circulation 2004;109:1930–2.
4. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004;109:1366–70.
5. Fröbert O, Lagerqvist B, Carlsson J, Lindbäck J, Stenestrand U, James SK. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). J Am Coll Cardiol 2009;53:1660–7.
6. Machecourt J, Danchin N, Lablanche JM, et al., EVASTENT Investigators. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. J Am Coll Cardiol 2007;50: 501–8.
7. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
8. Katoh H, Shite J, Shinke T, et al. Delayed neointimalization on sirolimus-eluting stents: 6-month and 12-month follow up by optical coherence tomography. Circ J 2009;73:1033–7.
9. Moore P, Barlis P, Spiro J, et al. A randomized optical coherence tomography study of coronary stent strut coverage and luminal protrusion with rapamycin-eluting stents. J Am Coll Cardiol Intv 2009;5: 437–44.
10. Matsumoto D, Shite J, Shinke T, et al. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. Eur Heart J 2007;28:961–7.
11. Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia. A serial intravascular ultrasound study. Circulation 1997;95:1366–9.
12. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109:2273–8.
13. Jiménez-Quevedo P, Sabaté M, Angiolillo DJ, et al.; DIABETES Investigators. Vascular effects of sirolimus-eluting versus bare-metal stents in diabetic patients: three-dimensional ultrasound results of the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. J Am Coll Cardiol 2006;47:2172–9.
14. Patterson C, Mapera S, Li HH, et al. Comparative effects of paclitaxel and rapamycin on smooth muscle migration and survival: role of AKT-dependent signaling. Arterioscler Thromb Vasc Biol 2006;26: 1473–80.
15. Aranson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. J Am Coll Cardiol 1996;27: 528–35.
16. Kanazaki T, Shinomiya M, Ueda S, Morizaki N, Saito Y, Yoshida S. Enhanced arterial intimal thickening after balloon catheter injury in diabetic animals accompanied by PDGF β receptor overexpression. Eur J Clin Invest 1994;24:377–81.
17. Kirstein M, Brett J, Radoff S, Ogawa S, Stern D, Vlassara H. Advanced protein glycosylation induces selective transendothelial human monocyte chemotaxis and secretion of PDGF: role in vascular disease in diabetes and aging. Proc Natl Acad Sci U S A 1990;87: 9010–4.
18. Takano M, Yamamoto M, Inami S, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. J Am Coll Cardiol 2009;55:26–32.
19. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.

Key Words: diabetes mellitus ■ optical coherence tomography ■ sirolimus-eluting stent(s) ■ vascular response.