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Comparison of Neoatherosclerosis and Neovascularization Between Patients With and Without Diabetes

An Optical Coherence Tomography Study

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ABSTRACT

OBJECTIVES This study aimed to investigate the characteristics of neoatherosclerosis (NA) in patients with diabetes mellitus (DM) after drug-eluting stent (DES) implantation using optical coherence tomography.

BACKGROUND NA is an important substrate for stent failure. In vivo NA characteristics in DM patients have not been investigated.

METHODS A total of 397 patients with 452 DES who underwent follow-up optical coherence tomography examination after DES implantation were enrolled. Characteristics of NA were compared between DM and non-DM patients. Neovascularization was defined as signal-poor holes or tubular structures with a diameter of 50 to 300 μm.

RESULTS A total of 123 DES with NA lesions in 115 patients were identified. The incidence of NA was similar between DM and non-DM patients (29.6% vs. 28.6%; $p = 0.825$). Compared with the non-DM group, neovascularization was more frequently observed in the DM group (55.1% vs. 32.4%; $p = 0.012$). The multivariate logistic model demonstrated that DM (odds ratio: 3.00; 95% confidence interval: 1.31 to 6.81; $p = 0.009$) and follow-up duration (odds ratio: 1.03; 95% confidence interval: 1.02 to 1.05; $p < 0.001$) were the independent predictors for neovascularization in NA lesions. DM patients with glycated hemoglobin ≥7.0% had a higher prevalence of thin-cap fibroatheroma compared with those with glycated hemoglobin <7.0% (40.0% vs. 8.3%; $p = 0.01$).

CONCLUSIONS The incidence of NA was similar between patients with and without DM. Neovascularization in NA lesions was more frequent in those with DM. Poorly controlled DM patients had a higher incidence of thin-cap fibroatheroma, compared with those with well-controlled DM. (J Am Coll Cardiol Intv 2015;8:1044–52)

Emerging evidence suggests in-stent neoatherosclerosis (NA) is an important substrate for both in-stent restenosis and late stent thrombosis (1). Tian et al. (2) assessed the characteristics of neointimal hyperplasia after drug-eluting stent (DES) implantation in patients with diabetes mellitus (DM) by optical coherence tomography (OCT) and found that glycated hemoglobin (A_{1C}) levels in DM patients

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contributed to the development of neointimal hyperplasia and in-stent NA. However, the difference in NA characteristics after DES implantation in patients with and without DM has not been reported. OCT is an emerging intravascular imaging modality with a resolution of 10 to 20 μm. It can characterize microscopic morphological features of atherosclerotic plaques, such as fibrous cap thickness, thin-cap fibroatheroma (TCFA), macrophage accumulations, neovascularization, thrombus, and calcification (3). The present study aimed to investigate characteristics of NA in DM patients after DES implantation using OCT imaging.

ABBREVIATIONS AND ACRONYMS

A_{1C} = glycated hemoglobin
CKD = chronic kidney disease
DES = drug-eluting stent(s)
DM = diabetes mellitus
MGH = Massachusetts General Hospital
NA = neoatherosclerosis
OCT = optical coherence tomography
TCFA = thin-cap fibroatheroma

METHODS

STUDY POPULATION. The Massachusetts General Hospital (MGH) OCT registry is a multicenter registry of patients undergoing OCT of the coronary arteries and includes 20 sites across 6 countries. Any patient who underwent an OCT procedure was eligible for the registry. For the present study, we identified 486 patients with 554 previously implanted DES from the MGH OCT between August 2010 and November 2013. Among these patients, we excluded those with <6 months of follow-up OCT examination (n = 77). Stents with poor OCT image quality (n = 12) were also excluded. A total of 452 DES in 397 patients were included in the final analysis. The presence of lipid-laden neointima or calcification inside of the stents was defined as NA in the present study. Subjects were assigned to the DM group if they were receiving an oral hypoglycemic agent or insulin or if they had a known fasting blood glucose value ≥126 mg/dl or post-prandial 2-h blood glucose value ≥200 mg/dl. NA characteristics were compared between DM and non-DM subjects. Moreover, DM subjects were divided into 2 groups based on A_{1C} level <7.0% or ≥7.0%, and NA characteristics were compared. The study protocol was approved by the institutional review board at each site, and written informed consent was obtained from all patients. The MGH OCT Registry is registered on ClinicalTrials.gov (NCT01110538).

QUANTITATIVE CORONARY ANGIOGRAPHY. Coronary angiograms were analyzed using off-line software (CAAS 5.10.1, Pie Medical Imaging BV, Maastricht, the Netherlands). Diameter stenosis, reference diameter, and minimum lumen diameter were measured. Angiographic restenosis was defined as a diameter stenosis >50% at follow-up angiography.

OCT IMAGE ACQUISITION. The time-domain OCT system (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc., Westford, Massachusetts) or the frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) was used in this study. In the M2/M3 system, an occlusion balloon (Helios, LightLab Imaging) was inflated proximal to the stent at 0.4 to 0.6 atm during image acquisition. The optical probe was automatically pulled back from distal to proximal at a rate of 1.0 to 3.0 mm/s, and saline was continuously infused from the tip of the occlusion balloon. In the C7XR system, a 2.7-F OCT imaging catheter was carefully advanced distal to the stent. The automated pullback was performed at 20 mm/s, while blood was displaced by a short injection of contrast media or Dextran through the guiding catheter (4). All OCT images were stored digitally, deidentified, and submitted to the MGH laboratory for off-line analysis.

OCT IMAGE ANALYSIS. Cross-sectional OCT images were analyzed at 1-mm intervals. For quantitative analysis, stent and luminal cross-sectional areas (CSAs) were measured, and neointimal hyperplasia (NIH) CSA was calculated as: stent CSA − luminal CSA. Mean values were reported in this study. The thickness of neointimal hyperplasia was measured as the distance between the endoluminal surface of the neointima and the strut. An uncovered strut was defined when no material covering a strut was identified. The percentage of uncovered struts in each stented lesion was calculated as: ([number of uncovered struts/total number of struts in all cross sections of the lesion] × 100). For qualitative analysis, a lipid was defined as a diffusely bordered, signal-poor region with rapid signal attenuation. Lipid-laden neointima was defined as a neointima with lipid (5) (**Figure 1**). Calcification was defined as a clearly delineated, signal-poor region with low backscatter. TCFA was defined by lipid-rich neointima with cap thickness ≤65 μm and an angle of lipidic tissue ≥180° (6). Neovascularization was defined as a signal-poor hole or tubular structure with a diameter ≥50 and ≤300 μm that was present on at least 3 consecutive frames (7). Disrupted neointima was a break in the fibrous cap that connected the lumen with the underlying lipid pool (8). Thrombus was a mass protruding into the vessel lumen, discontinuous from the surface of the vessel wall and with a dimension ≥250 μm (9).

OCT images were analyzed at the MGH OCT core laboratory by 2 independent investigators blinded to patient information (L.G., T.S.). All cross-sectional