Comparison of Vascular Response to Statin Therapy in Patients With Versus Without Diabetes Mellitus

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Diabetes mellitus (DM) increases cardiovascular morbidity and mortality. A statin is routinely prescribed to patients with DM. However, whether a statin therapy is equally effective in plaque stabilization in DM patients compared with non-DM patients is unknown. A total of 117 lipid-rich plaques were imaged in 90 patients (54 plaques in 41 DM patients and 63 plaques in 49 non-DM patients) with coronary artery disease, those who were treated with a statin and underwent serial optical coherence tomography imaging were included in this study (mean follow-up period, 362 ± 38 days). The changes in minimum fibrous cap thickness (FCT) and lipid index between baseline and 1-year follow-up were compared between the 2 groups. Minimum FCT increased and lipid index decreased with statin therapy in both groups. No significant differences were observed in percent changes of minimum FCT (p = 0.796) and lipid index (p = 0.336) between DM and non-DM patients. Statin therapy induced a significant increase in FCT and a significant decrease in lipid index in both groups. Vascular response to statin therapy was similar between the 2 groups irrespective of DM status. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:1559−1564)**

Diabetes mellitus (DM) is one of the major risk factors for cardiovascular morbidity and mortality.[1] Although lipid-lowering statin therapy is recommended for the primary prevention of atherosclerotic cardiovascular diseases in DM patients,[2] it has been reported that statin therapy may not be as effective in DM patients as in non-DM patients.[3] Optical coherence tomography (OCT) enables detailed characterization of coronary plaque features including fibrous cap.[4] Fibrous cap thickness (FCT) is probably most important for plaque vulnerability.[5,6] Recent studies using OCT have demonstrated that statin therapy increases FCT, thereby stabilizing the plaque.[7,8] However, whether statin therapy is as effective in DM patients as in non-DM patients for plaque stabilization has not been studied. This study investigates the changes in FCT after statin therapy using OCT, and compares the plaque response to statin therapy between patients with and without DM.

Methods

The study subjects were selected from 2 datasets: the Massachusetts General Hospital OCT Registry (ClinicalTrials.gov: NCT01110538) and a prospective randomized trial entitled "Evaluation of Statin-induced Lipid-rich Plaque Progression by Optical Coherence Tomography (OCT) Combined With Intravascular Ultrasound (IVUS)" (ClinicalTrials.gov: NCT01023607).[9] Because the former was not a prospective study, we selected the subjects who had repeat procedure between 6 and 18 months. From the prospective study, we only chose the 12-month OCT images. Among these patients, we selected those who had plaques with >50% area stenosis compared with the reference segment, and lipid arc ≥1 quadrant on OCT and identified serial imaging of 117 target plaques in 90 patients.

Patients were assigned to the DM group if they were receiving insulin or oral hypoglycemic agents, had fasting plasma glucose level ≥126 mg/dl, 2-hour plasma glucose level ≥200 mg/dl by oral glucose tolerance test, classic symptoms with random plasma glucose level ≥200 mg/dl, or hemoglobin A1c level ≥6.5%.[10] The intensity of statin treatment was classified as high, moderate, or low intensity, according to published guidelines.[2]

OCT images were acquired using frequency domain or time domain OCT after intracoronary administration of 100 to 200 μg of nitroglycerin. Qualitative and quantitative analyses were performed at 1-mm intervals. The morphologic classification of plaques was based on the previously established criteria.[11] Serial OCT images at baseline and follow-up were reviewed side by side, and target lesions were matched using the landmarks, such as side branches, calcifications, and stents. Minimum FCT was measured at its thinnest part 3 times and the average value was calculated. In addition, we applied a previously validated computer

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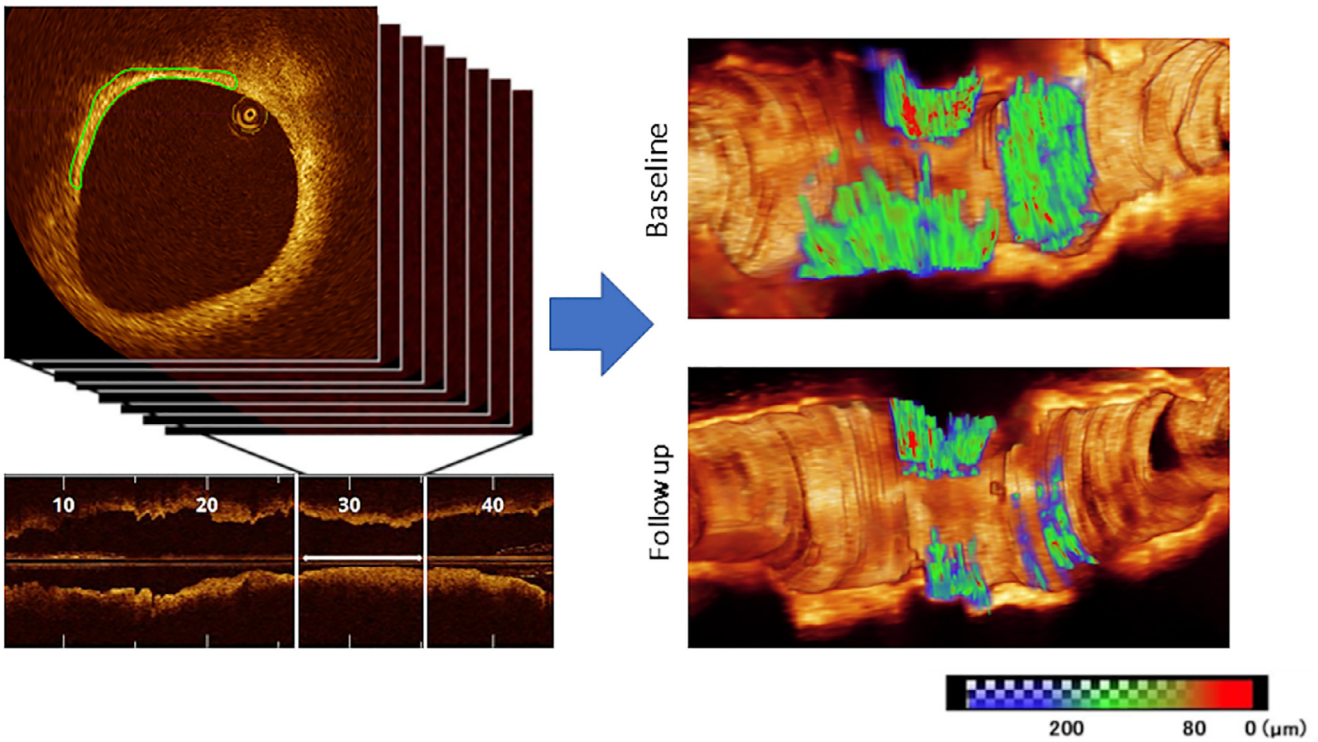

Figure 1. Representative 3-dimensional area measurement and images of the change in thin-cap area during follow-up. The fibrous cap was semiautomatically segmented (*green circle* in *left upper panel*) by the validated computer algorithm in all frames along the entire plaque. With the fully segmented fibrous cap, the algorithm quantified the thickness at each point of its luminal boundary. The thin-cap area was calculated as the product of the frame interval and the arc length of thin fibrous cap (<200 μm) summed over involved frames. Representative 3-dimensional images of the change in thin-cap area during follow-up (*right panel*).

algorithm to volumetrically assess the 3-dimensional fibrous cap and measured thin cap area (Figure 1).[8,12] The thin fibrous cap area was defined as the fibrous cap surface area with cap thickness <200 μm, in accordance with previous study.[8,13] Intraobserver and interobserver reproducibility values of the area measurement were good (intraclass correlation coefficients, 0.942 and 0.927, respectively).[8] Lipid length was measured on longitudinal view, and lipid index was calculated as the product of mean lipid arc and lipid length.[14] Macrophage infiltration and cholesterol crystals were defined as previously established criteria.[11]

Categorical data were expressed as absolute frequencies and percentages, and compared using the chi-square test. Continuous variables were expressed as mean ± SD for normally distributed variables and compared using the Student's *t* test. Comparisons of continuous measurements between baseline and follow-up were performed by paired *t* test. Patients in the DM group were younger compared with those in the non-DM group ($p = 0.040$), and the prevalence of current smoking in the non-DM group was higher than in the DM group ($p = 0.001$). To adjust the DM effect for those, multivariable regression analysis was performed. All differences were evaluated at a 5% level of significance ($p < 0.05$). All analyses were performed using SPSS Statistics 23.0 software (IBM Corp, Armonk, New York).

Results

Patient clinical characteristics are summarized in Table 1. Patients in the DM group were younger and had a significantly lower prevalence of smoking compared with those in the non-DM group. The laboratory findings are summarized in Table 2. Lipid panel as well as high-sensitivity C-reactive protein (hs-CRP) significantly decreased from baseline to follow-up in both groups. Figure 2 demonstrates that minimum FCT significantly increased, and lipid index significantly decreased from baseline to follow-up in both groups. Percent changes in minimum FCT and lipid index were similar in both groups (Figure 2). After adjusting for age and current smoking status, DM was not a significant predictor of the absolute and percent change in FCT ($p = 0.155$ and $p = 0.246$, respectively) and absolute and percent change in lipid index ($p = 0.396$ and $p = 0.511$, respectively). Quantitative and qualitative assessment of plaque morphology by OCT is summarized in Table 3. We selected 66 analyzable plaques for 3-dimensional fibrous cap area measurement (Figure 1). Fibrous cap area <200 μm significantly decreased from baseline (10.3 ± 11.0 mm^2) to follow-up (6.3 ± 8.1 mm^2; $p = 0.001$) in the DM group and from baseline (7.0 ± 7.4 mm^2) to follow-up (4.0 ± 5.4 mm^2; $p < 0.001$) in the non-DM group; however, the percent decrease was not different between the 2 groups.

Discussion

The main findings of this study are that FCT significantly increased with statin therapy at 1 year, and that the changes in FCT were not different between DM and non-DM patients. Statin therapy decreases cardiovascular

Table 1
Baseline characteristics

Variable	Diabetes mellitus		p Value
	Present (n = 41)	Absent (n = 49)	
Age (years)	53.1 ± 9.2	57.1 ± 9.1	0.040
Gender, men	29 (71 %)	37 (76 %)	0.610
Hypertension	29 (71%)	27 (55%)	0.128
Hyperlipidemia	19 (46 %)	28 (57 %)	0.307
Current smoker	13 (32%)	35 (71%)	0.001
Prior myocardial infarction	10 (24 %)	11 (23 %)	0.828
Presentation			0.211
Acute myocardial infarction	8 (19 %)	11 (23%)	
Unstable angina pectoris	22 (54 %)	32 (65%)	
Stable angina pectoris	11 (27%)	6 (12 %)	
Treatment			
Percutaneous coronary intervention	38 (93%)	43 (88%)	0.438
Follow up period (days)	368 ± 20	357 ± 47	0.179
Medications			
ACE-I/ARB	16 (39 %)	12 (24 %)	0.138
Dual antiplatelet therapy	31 (76 %)	36 (73%)	0.817
Statin naïve	36 (88 %)	39 (80 %)	0.298
Statin intensity			0.237
High	8 (19%)	13 (27%)	
Moderate	31 (76 %)	36 (73%)	
Low	2 (5 %)	0 (0 %)	

Values are numbers (%) or means ± SD.
Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg, or as having received antihypertensive drugs. Hyperlipidemia was defined as low-density lipoprotein level ≥140 mg/dl, or as having received treatment.

events,[2] and previous studies using intracoronary imaging techniques have shown the beneficial effects of statin therapy on atherosclerotic plaque. Grayscale intravascular ultrasound (IVUS) studies demonstrated the reduction of plaque volume.[15,16] An angioscopy study showed a decrease in yellow plaque color grade indicating plaque stabilization.[17] Serial near-infrared spectroscopy IVUS demonstrated that statin therapy reduces lipid content.[18] In

Table 2
Laboratory findings

Variable	Diabetes mellitus		p Value
	Present (n = 41)	Absent (n = 49)	
Total cholesterol (mg/dl)			
Baseline	194 ± 43	184 ± 34	0.191
Follow up	146 ± 43	144 ± 33	0.780
Absolute change	−48.0 ± 48.1*	−40.4 ± 45.2*	0.441
Low-density lipoprotein cholesterol (mg/dl)			
Baseline	104 ± 30	107 ± 27	0.653
Follow up	72.8 ± 32.9	71.8 ± 20.6	0.854
Absolute change	−31.1 ± 35.3*	−34.8 ± 29.5*	0.585
High-density lipoprotein cholesterol (mg/dl)			
Baseline	50.1 ± 13.7	45.5 ± 12.0	0.094
Follow up	46.9 ± 14.6	45.1 ± 13.2	0.353
Absolute change	−3.2 ± 14.4	−0.5 ± 13.1	0.526
Triglyceride (mg/dl)			
Baseline	208 ± 110	176 ± 97	0.147
Follow up	150 ± 74	126 ± 55	0.079
Absolute change	−58.1 ± 99.7*	−50.3 ± 77.6*	0.418
High sensitivity C-reactive protein (mg/dl)			
Baseline	9.6 ± 23.0	7.6 ± 26.6	0.732
Follow up	1.4 ± 1.7	1.7 ± 4.3	0.683
Absolute change	−7.9 ± 23.4*	−5.7 ± 29.1*	0.735

Values are numbers (%) or means ± SD.
* $p < 0.001$ between baseline and follow-up.

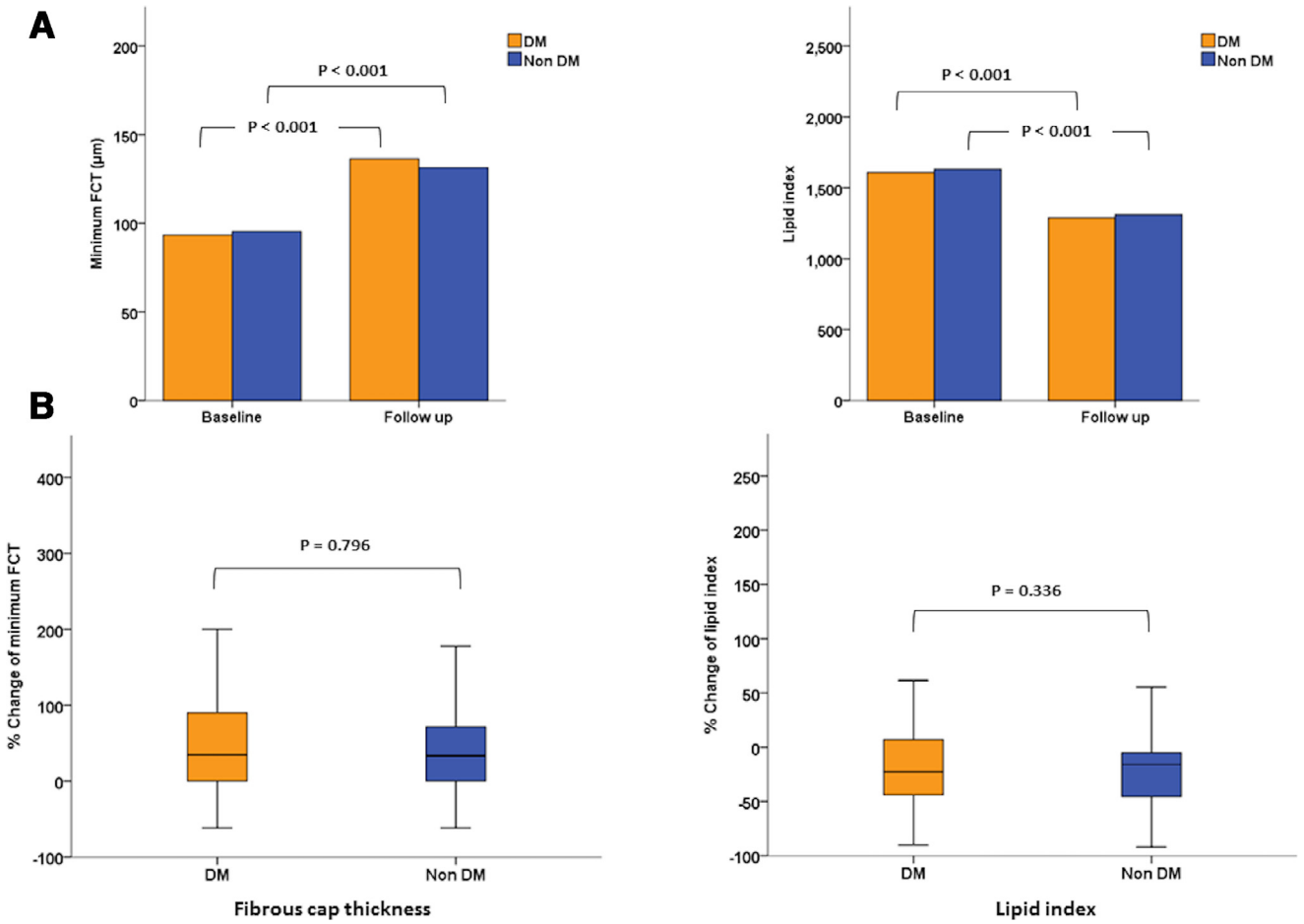

Figure 2. Comparisons of fibrous cap thickness (FCT) and lipid index between diabetes mellitus (DM) and non-DM. *(A)* Minimum FCT significantly increased from baseline to follow-up in both DM and non-DM groups ($p < 0.001$ and $p < 0.001$, respectively). Lipid index significantly decreased from baseline to follow-up in both groups ($p < 0.001$ and $p < 0.001$, respectively). *(B)* Percent change of minimum FCT and lipid index were similar between DM and non-DM groups ($p = 0.796$ and $p = 0.336$, respectively).

Table 3
OCT findings

Plaques	Diabetes mellitus		p Value
	Present (n = 54)	Absent (n = 63)	
Minimum fibrous cap thickness, μm			
Baseline	93.3 ± 39.4	95.4 ± 47.0	0.799
Follow up	136 ± 64	131 ± 61	0.675
Absolute change	43.0 ± 52.1*	36.0 ± 58.2*	0.501
Lipid index			
Baseline	1608 ± 1012	1631 ± 962	0.899
Follow up	1288 ± 987	1311 ± 991	0.904
Absolute change	−367 ± 780*	−321 ± 561*	0.707
Macrophage, n			
Baseline	40 (74%)	46 (73%)	0.897
Follow up	35 (65%)	39 (62%)	0.745
Cholesterol crystal, n			
Baseline	14 (26%)	13 (21%)	0.498
Follow up	8 (15%)	9 (14%)	0.935

Values are numbers (%) or means ± SD.
* $p < 0.001$ between baseline and follow-up.

addition, several recent OCT studies have demonstrated that statin therapy increases FCT and decreases lipid index, thereby stabilizing plaques.[7,8]

Although statin therapy is recommended for the prevention of cardiovascular diseases in DM patients,[2] the cardiovascular morbidity remains high.[19] The mechanism for the relative lack of efficacy is unclear. Studies using IVUS showed that plaque regression is less pronounced in DM patients than in non-DM patients.[3] A previous study using OCT demonstrated that, in response to statin, DM patients had a smaller increase in FCT and smaller decrease in lipid index compared with non-DM patients.[20] However, information on statin intensity and adherence was lacking in the study. Statin intensity and statin naïve status before treatment are known to influence the vascular response to statin therapy,[8,9] and this information is likely to be essential to compare the efficacy of statins.

In the current study, we sought to compare the effects of statin therapy for plaque stabilization, as measured by FCT and lipid burden. Among several microstructures of a plaque, the fibrous cap is probably the most important structural determinant of plaque vulnerability. In the previous OCT report, the non-DM group tended to have thinner fibrous caps than DM group at baseline, and non-DM group had a larger increase in FCT compared with DM group.[20] In contrast, there was no significant difference in FCT between the 2 groups both at baseline and at follow-up, and our study demonstrated that plaque stabilization by statin therapy was comparable between patients with and without DM. One possible explanation for this discrepancy is that, because thinner fibrous caps may have the potential to increase their thickness by statin therapy,[7] the thinner fibrous caps in the non-DM group might have had better response than in the DM group in the earlier study. Another previous study with a larger number of patients showed that DM patients tended to have thinner FCT compared with non-DM patients,[14] consistent with our study.

Plaque vulnerability is closely associated with vascular inflammation, and matrix metalloproteinase (MMP), produced by activated macrophages, which induces collagen breakdown in the fibrous cap.[21] Statin therapy stimulates collagen synthesis by inhibiting MMPs.[7] In DM patients, cytokines enhance production of MMPs and decrease collagen synthesis,[22] and thus FCT tended to be thinner.[14] The prevalence of smoking was higher in the non-DM group in our study. Smoking is associated with increased activity of MMPs, potentially resulting in increased collagen breakdown and thinning of fibrous caps.[23,24] The lower prevalence of smoking in the DM group might have favorably affected the increase in FCT. Our results are further supported by a more sophisticated analysis algorithm using 3-dimensional measurements of fibrous cap structure (Figure 1). Previous studies evaluated FCT only at 1 visually selected area. Single-point measurements are insufficient to explain the 3-dimensional remodeling of the fibrous cap in response to statin therapy. In contrast, the 3-dimensional measurements generate full-segmentation of the fibrous cap boundaries, which promise a characterization of the fibrous cap morphology without requiring precise matching of the cross sections of the plaque as required by the conventional measurement of minimum FCT.[12] Even with this objective method, we were not able to detect significantly different changes in minimum FCT and thin fibrous cap area between the 2 groups.

Several limitations require acknowledgment. First, the Massachusetts General Hospital (MGH) OCT Registry is a multicenter, prospective registry for all comers without strict inclusion criteria or guidelines for OCT image acquisition. Follow-up OCT was not mandated in the registry. In this study, we retrospectively selected the cases that had follow-up OCT imaging. Thus, selection bias could not be excluded. Second, although >80% patients were statin naïve, data on the duration of statin therapy before baseline OCT imaging was not recorded in the remaining 20% of nonstatin naïve patients. Third, despite >70% of patients having acute coronary syndrome (ACS), the proportion of prescribed high-intensity statin was <30%. Most subjects were enrolled in Asia and high intensity statin was less frequently used in Asia. In fact, the highest approved dose of atorvastatin in Japan is 20 mg/day. Fourth, data on the duration of DM and the specific types of hypoglycemic agents were not collected in our registry.

Disclosures

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