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Comparison of Coronary Plaque Characteristics between Diabetic and Non-diabetic Subjects: an *in vivo* Optical Coherence Tomography Study

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Abstract

Aims—Postmortem series have reported that subjects with diabetes mellitus have coronary plaques with larger necrotic cores and increased macrophage infiltration. Optical coherence tomography (OCT) is a high-resolution imaging modality that allows *in vivo* characterization of atherosclerotic plaques. Using OCT imaging, we compared *in vivo* plaque characteristics between diabetic and non-diabetic subjects.

Methods—Sixty-three patients undergoing cardiac catheterization were enrolled. OCT imaging was performed in culprit coronary arteries. Assessment of plaque lipid content, fibrous cap thickness and frequency of thin-cap fibroatheroma were made independently. Macrophage density was determined from the optical signal within fibrous cap.

Results—Eighty-two plaques in total were imaged (19 diabetic vs 63 non-diabetic). There were no significant differences in frequency of lipid-rich plaques (68% vs 71%; $P=0.78$), thin-cap fibroatheroma (29% vs 36%; $P=0.76$) or minimum fibrous cap thickness (66.6 vs 62.9 μm ; $P=0.87$) between diabetic and non-diabetic patients. Fibrous cap macrophage density was higher in lipid-rich plaques ($P=0.01$) but showed no difference between diabetic and non-diabetic patients (5.94% vs 5.94%; $P=0.37$).

Conclusions—There were no significant differences in culprit vessel plaque characteristics between diabetic and non-diabetic patients presenting with coronary artery disease. This represents the first study to characterize coronary plaques in diabetic patients using OCT.

Keywords

coronary plaque; diabetes mellitus; optical coherence tomography; thin-cap fibroatheroma

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Introduction

Patients with diabetes mellitus (DM) are characterized by increased morbidity and cardiovascular complications compared to non-diabetic patients [1,2]. Diabetic patients have more diffuse and severe coronary artery disease than non-DM population, resulting in worse outcomes after acute coronary syndromes [3,4], percutaneous coronary intervention [1,5] and surgical revascularization [1,6]. The cause of this difference is not well understood but may reflect metabolic abnormalities that predispose to atherosclerotic plaque disruption and thrombus formation [7,8]. Histopathological studies suggest that rupture of an existing 'vulnerable plaque' or thin-cap fibroatheroma (TCFA) is responsible for the majority of acute coronary syndromes or sudden cardiac deaths [9-11]. Due to their insidious nature, there is great interest in identifying these vulnerable plaques in advance of rupture. The features of TCFA include a thin fibrous cap ($<65\text{ }\mu\text{m}$) overlying necrotic core and increased macrophage infiltration [10,11]. Postmortem series have reported that DM subjects who die suddenly had plaques with larger necrotic cores and increased macrophage infiltration compared to non-DM subjects [12]. However, limited data is available on the *in vivo* appearance of coronary plaques in DM patients because of the lack of sensitive imaging modalities that could accurately define plaque morphology.

Optical coherence tomography (OCT) is an optical analogue of intravascular ultrasound that allows high-resolution ($\approx 10\text{ }\mu\text{m}$) tomographic intra-arterial imaging [13-17]. The OCT characteristics of various atheromatous plaque components have been validated previously in a histology-controlled study [16]. However no *in vivo* study to date has assessed detailed plaque morphology in diabetic patients. Our objective was to compare *in vivo* plaque characteristics using OCT between DM and non-DM subjects with symptomatic coronary artery disease. Specifically, we intended to assess differences in lipid content, fibrous cap thickness and macrophage density, and frequency of TCFA.

Methods

Study population

We enrolled prospectively patients undergoing coronary angiography who had identifiable culprit lesions in native coronary arteries. Subjects were excluded if they had significant left main disease, congestive heart failure, renal insufficiency (serum creatinine $>1.8\text{ mg/dL}$), required emergency angioplasty, or had severely tortuous or calcified culprit arteries. Patients with DM were identified based on clinical history of DM or insulin/oral hypoglycemic agents used. The institutional review board approved the study, and all patients provided written informed consent before participation.

Lesion identification

The culprit lesion for each patient was determined using coronary angiography and corroborated with information from the patient's electrocardiogram, nuclear or echocardiographic stress test and ventriculogram. When present, additional lesions within the culprit vessel that exceeded 30% diameter stenosis were also imaged.

OCT image acquisition

We performed intravascular OCT imaging as previously described [13]. Briefly, following administration of 100–200 μg of intra-coronary nitroglycerin, a 3.2-F OCT catheter was advanced through a guiding catheter over a coronary guidewire to the culprit lesion. Images were obtained at 4 frames/sec during intermittent saline flushes to transiently displace blood. Three locations were imaged per plaque: area of greatest stenosis or ulceration, distal and

proximal shoulder regions. Images were stored digitally for off-line analysis by 2 independent investigators using previously validated criteria for OCT plaque characterization [16]. Plaque lipid content was semi-quantified as number of involved quadrants and considered lipid-rich if present in two or more quadrants. Fibrous cap thickness was measured at the thinnest point overlying a lipid pool. Thin-cap fibroatheroma was defined as a lipid-rich plaque with fibrous cap thickness $<65\ \mu\text{m}$ [11]. Fibrous cap macrophage density was evaluated in plaques with lipid pool as previously described [14,18]. Presence of plaque disruption, calcification or thrombosis was noted.

Statistical analysis

Continuous variables were reported as mean $\pm$ SD or median (interquartile range). Baseline and plaque characteristics were compared using χ^2 , Fisher exact, Mann-Whitney or Student's *t* tests as appropriate. As the distribution of fibrous cap thickness was skewed to the right, natural logarithmic transformation, which normalized the distribution, was used for correlation analysis. All analysis was performed using SPSS version 14 (SPSS Institute Inc). A *P*-value <0.05 was required for statistical significance.

Results

Baseline characteristics

A total of 63 patients were enrolled: 16 diabetic (5 insulin therapy: 9 oral hypoglycemic medication) and 47 non-diabetic. Baseline characteristics were similar apart from incidence of hypertension ($P=0.02$) (Table 1). The coronary risk factors, clinical syndromes and extent of disease were similar between both groups.

Assessment of coronary plaque characteristics

All 63 patients underwent OCT imaging: 1 plaque was imaged in 44 patients (13 diabetic: 31 non-diabetic) and 2 plaques within the same vessel were assessed in 19 patients (3 diabetic: 16 non-diabetic). Eighty-two coronary plaques in total were evaluated (19 diabetic: 63 non-diabetic). The OCT findings are summarized in Table 2. Lipid-rich plaques were identified in majority of patients but there was no significant difference in the frequencies between DM and non-DM patients (68% vs 71% respectively; $P=0.78$). Incidence of calcification, thrombus and plaque disruption were also similar. The frequency of TCFA (Figure 1) and minimum fibrous cap thickness between the 2 groups were not significantly different (Table 2). Fibrous cap macrophage density was higher in lipid-rich plaque (Figure 2A) and correlated inversely with minimum fibrous cap thickness (natural logarithm) ($r=-0.48$, $P=0.004$). However, no significant differences in macrophage densities were found between DM and non-DM patients (5.94% vs 5.94%; $P=0.37$; see Figure 2B). Differentiating plaques into culprit or remote site plaques did not alter the findings.

All imaging procedures were performed without complications or adverse events.

Discussion

This is the first *in vivo* study to evaluate detailed plaque features in patients with DM using OCT. We have assessed critical aspects of culprit vessel plaque characteristics in diabetic patients including lipid pool, fibrous cap thickness and macrophage density and have found no evidence to indicate a significant association with DM. These findings suggest that plaque morphology of the culprit vessel in coronary artery disease is not influenced by diabetic status.

Coronary atherosclerosis is more prevalent and severe in patients with DM [2,19,20]. They experience more extensive disease burden, higher incidences of myocardial infarction, multi-

vessel and left main coronary disease, and higher mortality [12,21,22]. Most acute coronary syndromes are attributed to sudden luminal thrombosis as a result of plaque rupture, erosion or calcified nodules [11]. It has been postulated that TCFA is the precursor lesion of plaque rupture, and they are indeed frequently observed in subjects who die suddenly in postmortem studies [10]. Few studies however have explored the link between plaque morphology and DM. Coronary angiography in diabetic patients with unstable angina found a higher incidence of plaque ulceration and thrombosis [23]. Burke *et al* reported that sudden cardiac death in diabetic subjects was associated with more extensive atherosclerosis, greater plaque burden, necrotic core size and inflammatory response [12]. Infiltration of coronary plaques by macrophages may result in expression of proteolytic enzymes that weaken the fibrous cap and ultimately promote plaque disruption [24]. Coronary tissue from diabetic patients who had undergone directional coronary atherectomy has also been shown to exhibit larger lipid content and macrophage infiltration [25]. Thus it would be tempting to speculate from these preliminary data that increased incidence of ‘vulnerable plaques’ in diabetic patients may account for the difference in clinical outcomes.

However, we were not able to detect any significant differences in the coronary plaque characteristics in this present study. Notably, frequency of TCFA and fibrous cap macrophage density, a marker of plaque inflammation were similar. This discrepancy with the above *ex vivo* studies may be explained in part by the different study cohort as pathological studies potentially include higher proportion of acute coronary syndrome patients. More importantly, we provided detailed *in vivo* rather than *ex vivo* evaluation of plaque characteristics. These results corroborate the findings by Rodriguez-Granillo *et al*, who did not demonstrate any association between DM and “intravascular ultrasound-derived TCFA” [26]. Potential contributory factors such as impaired vasomotor, platelet or hematological function and the abnormal metabolic state that accompanies diabetes may thus play a more influential role in prognosis [8].

Although intravascular ultrasound is the most widely used invasive imaging modality to assess coronary arteries *in vivo*, OCT was shown to be more sensitive in plaque detection and characterization in post mortem studies as well as in patients presenting with acute myocardial infarction [27,28]. The incorporation of spectral analysis of radiofrequency ultrasound signals in recent intravascular ultrasound consoles, also known as virtual histology, can potentially allow indirect assessment of plaque composition [26]. Indeed, a recent retrospective study by Nasu *et al* using virtual histology reported larger necrotic core and dense calcium within the target vessels in diabetic patients compared to non-diabetic patients [29]. However, a major limitation is the insufficient axial resolution of this technology to assess fibrous cap thickness, a key feature of TCFA. Hence comparative studies with histopathology are required and prospective studies are also currently underway to correlate virtual histology derived plaque characteristics with clinical outcome.

Limitations

This study has several limitations. With our current OCT system, long arterial segment imaging was not possible and we may have failed to image an area of importance such as an exact rupture site. Limited axial penetration of OCT also excludes visualization of deep structures, although important morphological determinants of plaque vulnerability are superficial and usually within the imaging range. Enhancements to OCT technology are anticipated to improve penetration depth and provide significantly faster acquisition rates [30,31]. Our study also primarily evaluated culprit vessels in patients who were symptomatic from coronary artery disease and did not include patients with clinically silent disease. Lastly, the size of the study was small and confounding factors such as hypertension may have influenced the results although this was not evident in post-hoc analysis.

Conclusion

We have demonstrated that in patients with coronary artery disease, there is no significant association in culprit vessel plaque characteristics with DM. This suggests that other factors rather than local plaque properties account for the poor cardiovascular outcomes in the diabetic population, and further studies are warranted to explore the underlying mechanism.

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Figure 1.

In *vivo* optical coherence tomography image of a thin-cap fibroatheroma. Signal-poor regions (L) surrounded by diffuse borders and separated by signal-rich layer are consistent with lipid pools. Lipid is present in half of the whole circumference. Thin-cap fibroatheroma is identified by a thin fibrous cap (black arrow, ↑) overlying a large lipid-rich plaque. Guide-wire artefact is seen at 10 o'clock position (*).

Figure 2. Macrophage density of coronary plaque fibrous caps in (A) lipid-rich and non-lipid rich plaques; and (B) diabetic and non-diabetic subjects. Macrophage density was higher in lipid-rich plaques* but did not differ between diabetic and non-diabetic subjects. Median $\pm$ interquartile range. * $P=0.01$.

Table 1

Baseline characteristics

	Diabetes	No Diabetes	<i>P</i>
Number of patients, <i>n</i>	16	47	
Age	60 ± 8	59 ± 10	0.44
Gender, female/male	2 / 14	8 / 39	1.00
Coronary risk factors, <i>n</i> (%)			
Hypertension	13 (81)	21 (45)	0.02
Hyperlipidemia	14 (88)	34 (72)	0.32
Smoking history	11 (67)	39 (83)	0.29
Family history of coronary artery disease	7 (44)	29 (62)	0.25
Prior coronary revascularization	5 (31)	7 (15)	0.16
Multi-vessel disease	10 (63)	19 (40)	0.15
Clinical presentation, <i>n</i> (%)			0.80
Stable angina	5 (31)	12 (26)	
Non ST-elevation acute coronary syndrome	5 (31)	19 (40)	
ST-elevation myocardial infarction	6 (38)	16 (34)	

Values are mean ± SD or *n* (%).

Table 2

Coronary plaque characteristics

	Diabetes	No Diabetes	<i>P</i>
Number of plaques, <i>n</i>	19	63	
Number of lipid quadrants, <i>n</i>			0.84
0	2	4	
1	4	14	
2	6	24	
3	5	13	
4	2	8	
Lipid-rich plaque (≥ 2 quadrants), <i>n</i> (%)	13 (68)	45 (71)	0.78
Fibrous cap thickness, μm *	66.6 (71.4)	62.9 (57.3)	0.87
Presence of thin-cap fibroatheroma (<i>n</i> =67)	4 (29)	19 (36)	0.76
Plaque disruption / rupture	3	9	1.00
Calcification	5	8	0.17
Thrombus	5	8	0.17
Culprit vessel, <i>n</i> (%)			0.89
Left anterior descending artery	12 (63)	38 (60)	
Left circumflex artery	4 (21)	12 (17)	
Right coronary artery	3 (16)	13 (21)	

Values are expressed as mean, *n* (%) or

* median (interquartile range)