Impact of Diabetes Mellitus on Angiographically Silent Coronary Atherosclerosis
—— An Intravascular Ultrasound Study ——

Hiroya Tamada, MD; Hideo Nishikawa, MD*; Sei Mukai, MD*; Morimichi Setsuda, MD*; Mamoo Nakamura, MD*; Hiroyuki Suzuki, MD; Takahiro Oonishi, MD*; Yutaka Kakuta, MD*; Alan C. Yeung, MD**; Takeshi Nakano, MD

Constrictive remodeling occurs in significant atherosclerotic lesions of the diabetic patient, but the impact of diabetes mellitus (DM) on the angiographically normal coronary artery is still unclear. Morphometric analysis using intravascular ultrasound (IVUS) prior to intervention evaluated 54 sites in 33 DM patients and 106 in 62 non-diabetic patients. Vessel area (VA) and lumen area (LA) were measured at angiographically normal sites in the vessel. Plaque area (PA) was calculated as VA – LA. Percentage plaque area (%PA) was calculated as PA ÷ VA. Even in the angiographically normal site, mild coronary atherosclerosis was detected by IVUS in both groups. In the patients with DM, VA and LA were significantly smaller than in the non-diabetic patient (15.5 vs 17.8 mm², p<0.01; and 10.1 vs 12.2 mm², p<0.01 respectively), whereas %PA was similar (34.5 vs 31.6%). At angiographically normal sites where mild coronary atherosclerosis is detected by IVUS, the coronary artery of diabetic patients is smaller than that of the non-diabetic. These results suggest impaired compensatory enlargement or some other constrictive mechanism has already occurred in the early stages of coronary atherosclerosis in patients with DM. (Circ J 2003; 67: 423–426)

Key Words: Diabetes mellitus; Coronary remodeling; Intravascular ultrasound

Angiographic studies of patients with both symptomatic and asymptomatic diabetes mellitus (DM) have documented more diffuse coronary artery lesions than in non-diabetic subjects, as well as earlier onset and accelerated progression of coronary artery disease.1,2 Although coronary angiography is the standard modality for assessing coronary artery disease, it identifies only intra-luminal changes and does not provide data about the arterial wall.3

Intravascular ultrasound (IVUS) has been used to give detailed insight of coronary atherosclerosis.4–6 One study reported that IVUS can more sensitively detect atherosclerosis in angiographically normal coronary artery segments7 and both pathologic and IVUS studies have revealed that the process of lesion formation in coronary artery disease is complex. In general, adaptive positive remodeling of diseased atherosclerotic arterial segments (an increase in arterial dimensions) compensates for plaque accumulation, and delays lumen compromise until the lesion occupies, on average, more than an estimated 40–50% of the potential area within the external elastic membrane.8,9 Recent IVUS studies have also indicated that changes in arterial dimensions occur along a bi-directional continuum ranging from adaptive (positive) remodeling to arterial shrinkage (negative remodeling).10,11 Several studies have reported that arterial shrinkage contributes to the severe atherosclerotic lesions seen predominantly in DM.12,13 In diabetic patients, however, the stage of the atherosclerotic process at which this arterial shrinkage occurs has not been well investigated. Thus, the aim of this study was to investigate the influence of DM on the early stage of coronary atherosclerosis, using IVUS to interrogate angiographically normal segments of the diseased coronary artery.

Methods

Patient Population

Between April 1998 and September 1999, IVUS was performed prior to angioplasty in 95 consecutive patients with coronary artery disease (70 male, 64±10 years) who had angiographically normal segments within and proximal to the target artery, for which catheter intervention was planned for the significant stenosis. We selected 160 coronary segments that were the most visually ‘normal’ angiographic sites within 20 mm proximal to the target lesion, but distal to a major side branch (Fig 1). Patients whose target arteries were tortuous, bifurcated or angiographically calcified were excluded from the study. Non-dominant right coronary artery and small left circumflex artery were not enrolled. The study group consisted of 54 arterial sites in 33 diabetic patients and 106 sites in 62 non-diabetic patients. All diabetic patients had been either on diet/exercise alone or a combination of diet/exercise with medical treatment (insulin or oral hypoglycemic agents) for at least 1 year. DM was diagnosed if either a fasting blood glucose greater than 126 mg/dl or a random blood glucose
greater than 200 mg/dl was documented during the patient’s hospitalization. All other patients who did not fulfill these criteria were included in the non-diabetic group. The mean duration of diabetic therapy in this study was 13.4±7.4 years. Diet or exercise therapy was prescribed for 6 patients, hypoglycemic drugs for 23 patients and insulin therapy for 4 patients; these data were confirmed by patient interview and by a review of medical records. Written informed consent for IVUS was obtained from all subjects prior to the angioplasty procedure.

Angiographic Analysis

All pre-interventional cine-angiograms of the sites at which IVUS measurements were taken were analyzed using a computer-assisted, automated edge-detection algorithm (QCA-CMS Version 3.32, MEDIS medical imaging system, Leiden, The Netherlands) by a single angiographer who had no knowledge of the ultrasound results. The outer diameter of the contrast-filled catheter was used for calibration.

IVUS Imaging Protocol

All IVUS images were obtained using a commercially available imaging system (Boston Scientific, Natick, MA, USA) incorporating a single-element with either a 3.2F catheter (center frequency of 30 MHz) or a 2.6F catheter (center frequency of 40 MHz). After completion of angiography, the imaging catheter was introduced into the target artery through the 8F coronary guiding catheter over a 0.014 inch (0.36 mm) guide wire. To prevent possible vaso- spasm, intracoronary nitroglycerin (300 µg) was administered to all patients prior to the procedure. Under fluoroscopic guidance, the imaging catheter was advanced to the distal portion of the vessel and using auto-pullback (0.5 mm/s), ultrasound images were obtained and recorded on 0.5-inch SVHS videotape for quantitative data analysis. X-ray fluoroscopy was used to confirm that the imaging catheter was co-axial at the region of interest.

IVUS Analysis

Off-line analysis was performed by a single individual unaware of the clinical data after digitalization of the images using a computerized planimetry program (NetraIVUS™, ScImage, Inc, Los Altos, CA, USA). The frame of the region of interest corresponding to the angiographic normal segment was carefully selected using geometric landmarks. Using the images in the end-diastolic phase, morphometric analysis was performed. Vessel area (VA) was taken as the entire area surrounded by the external elastic membrane, defined by the medial-adventitial border and measured by tracing the outer border of the sonoluscent zone. Lumen area (LA) was taken as the area defined by the intimal-luminal border and measured by tracing the interface between the vessel lumen and the leading edge of the initial echogenic layer. Plaque area (PA) was calculated as VA – LA and percent plaque area (%PA) was obtained by dividing PA by VA.

Statistics

Results are expressed as mean ± SD. Statistical analysis was performed with StatView 4.5 (Abacus Concepts, Berkeley, CA, USA). Continuous variables were compared using Student’s unpaired t test. Categorical variables are presented as frequencies and were compared using the chi-square test. A value of p<0.05 was considered significant.

Results

Patient Characteristics

The baseline clinical and angiographic characteristics of the 2 groups are listed in Tables 1 and 2. There were no significant differences in clinical characteristics and both groups had similar distributions of studied vessels; however, the vessel diameter of angiographically normal segments at the sites where IVUS measurements were done, was smaller in the diabetic group than in the non-diabetic group.

Table 1 Baseline Characteristics of the Study Group (n=95)

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (n=53)</th>
<th>Non-diabetics (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. study sites</td>
<td>54</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±8.4</td>
<td>64±11</td>
<td>0.65</td>
</tr>
<tr>
<td>Men</td>
<td>25 (76%)</td>
<td>45 (73%)</td>
<td>0.77</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.61±0.15</td>
<td>1.65±0.18</td>
<td>0.28</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1±3.5</td>
<td>24.5±3.1</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15 (45%)</td>
<td>29 (47%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (70%)</td>
<td>39 (63%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 (58%)</td>
<td>36 (58%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>8 (24%)</td>
<td>22 (35%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Obesity</td>
<td>11 (33%)</td>
<td>17 (27%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%): BSA, body surface area; BMI, body mass index = weight/height²; CAD, coronary artery disease.

Table 2 Angiographical Characteristics of the Study Sites in the Stenotic Arteries (n=160)

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (n=54)</th>
<th>Non-diabetics (n=106)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMT</td>
<td>6 (11%)</td>
<td>17 (16%)</td>
<td>0.40</td>
</tr>
<tr>
<td>LAD</td>
<td>22 (41%)</td>
<td>48 (45%)</td>
<td>0.48</td>
</tr>
<tr>
<td>LCX</td>
<td>6 (11%)</td>
<td>14 (13%)</td>
<td>0.70</td>
</tr>
<tr>
<td>RCA</td>
<td>20 (37%)</td>
<td>27 (25%)</td>
<td>0.13</td>
</tr>
<tr>
<td>VD (QCA)</td>
<td>3.6±0.49</td>
<td>3.9±0.65</td>
<td>0.003</td>
</tr>
<tr>
<td>Normalized VD</td>
<td>2.2±0.36</td>
<td>2.4±0.43</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are number (%): LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex; RCA, right coronary artery; VD, vessel diameter (mm); Normalized VD, vessel diameter adjusted for body surface area.
Impact of DM on Coronary Atherosclerosis

Table 3  IVUS Characteristics of the Study Sites in the Stenotic Arteries

<table>
<thead>
<tr>
<th></th>
<th>Diabetics (n=54)</th>
<th>Non-diabetics (n=106)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel area (mm²)</td>
<td>15.5±3.9</td>
<td>17.8±5.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>10.1±3.0</td>
<td>12.2±4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Plaque area (mm²)</td>
<td>5.5±2.6</td>
<td>7.2±2.6</td>
<td>0.645</td>
</tr>
<tr>
<td>%Plaque area</td>
<td>35±12</td>
<td>32±11</td>
<td>0.104</td>
</tr>
</tbody>
</table>

Data are mean±SD.

Comparison of IVUS Measurements (Table 3)

Mean VA and mean LA in the diabetic patients were significantly smaller than in the non-diabetic subjects (15.5 vs 17.8 mm², p<0.01, and 10.1 vs 12 mm², p<0.01, respectively), whereas PA and %PA were similar (5.5 vs 5.7 mm², and 34.5 vs 31.6%, respectively). Because recent studies have indicated that IVUS parameters are smaller in women than in men, but not when normalized for body surface area (BSA)15 these parameters were also analyzed taking BSA normalization into account and the differences were still significant.

Impact of DM on IVUS Results

To further examine the impact of disease duration on vessel dimensions, patients with DM were further divided into those treated for 10 years or more, and those treated for less than 10 years. The mean duration of follow-up was 19.1±4.5 and 6.9±3.1 years, respectively. When compared with those treated less than 10 years, patients treated for longer had smaller VA (14.5±3.5 vs 16.9±4.1 mm², p=0.05), but there was no significant difference regarding LA between these 2 groups (≥10 years: 9.6±2.5 vs <10 years: 10.7±3.5 mm², p=0.18), although there was a trend of smaller LA in the ≥10 years group.

Impact of Diabetic Therapy on IVUS Results

As shown in Fig 2, patients treated with hypoglycemic agents or insulin had smaller VA and LA than those treated by diet/exercise therapy alone. Of note, diabetic patients requiring the use of hypoglycemic agents and/or insulin had a longer history of DM than those without medication.

Discussion

Patients with DM have an early and accelerated process of coronary atherosclerosis1,2,16 and coronary artery disease in the diabetic patient is thought to be more diffuse with a mortality rate 4- or 5-fold higher than non-diabetic patients, and with worse outcomes following angioplasty and stenting17-20 Several factors promote accelerated atherosclerosis in diabetics: (1) increased oxidation of low-density lipoproteins; (2) non-enzymatic glycation of vessel-wall proteins; (3) accelerated smooth muscle cell proliferation and migration; (4) hyperinsulinemia; (5) impaired fibrinolysis; and (6) increased platelet aggregation.21-25 Together, these processes may cause an increase in cholesterol synthesis, endothelial dysfunction, hyperplastic vasculopathy, microvascular disease, and a heightened pro-thrombotic state, all hallmarks of diabetic vascular disease.19-25

The presence of adaptive arterial remodeling in response to plaque accumulation has been documented for the superficial femoral arteries and carotid arteries by histopathology, high-frequency epicardial echocardiography, transcutaneous and intravascular US.9,26-28

In the development of compensatory arterial enlargement, previous reports have implicated 2 mechanisms: (1) stimulation of endothelium-dependent arterial dilatation in response to a local increase in wall shear stress caused by plaque deposition, and (2) passive bulging of the plaque as a result of degradation of the media and adventitia by the developing plaque. Arterial remodeling, however, is not a homogeneous process. Although adaptive remodeling appears to occur in most patients, inadequate arterial remodeling can also contribute to lumen compromise in the coronary arteries as well as in the superficial femoral arteries.10,11,29 Furthermore, it is well-documented that endothelium-dependent relaxation is impaired in diabetic patients.20

Our study suggests that the coronary arteries of diabetic patients are smaller than those of non-diabetics at the same angiographically normal segment of the artery with the significant stenosis. Vessel and lumen areas in the diabetic group were smaller despite similar plaque area when compared with the non-diabetic group. Mild atherosclerosis that had not been detected by angiography was observed by IVUS in both groups. In the present study, the coronary arteries of patients with long-term diabetes (≥10 years) were smaller than those of patients with short-term diabetes, which suggests that constrictive (negative) remodeling may have occurred in diabetic vessels during the early stages of the atherosclerotic disease process. Impairment of compensatory remodeling is one possible explanation for the smaller artery size, in the absence of an exaggerated plaque burden, found in the diabetic group. In diabetic patients, the compensatory vessel response to atherosclerosis is thought to be blunted and may lead to greater luminal stenosis in response to the same amount of atherosclerotic plaque accumulation. Primary arterial shrinkage (namely, a specific constrictive mechanism) has also been suggested as a potential mechanism of de novo stenosis formation. For patients in our study receiving oral hypoglycemic agents or insulin, the pathological process of coronary atherosclerosis development may be one of vessel shrinkage rather than an absence of adaptive remodeling; 80% of the present subjects were receiving insulin or oral hypoglycemic agents.
and because insulin is a known atherogenic agent, it is possible that the plasma insulin concentration affects the remodeling process in patients with DM31

Study Limitations

This study was a retrospective review and analysis of clinical and IVUS data derived from a large group of patients. Because of the selection and exclusion criteria, we were not able to enroll all consecutive patients presenting with DM and coronary artery. Thus, the degree of remodeling may not accurately reflect the entire cohort. The exclusion of tortuous segments, bifurcated sites and calcified plaques, which are all important and common features of remodeling in coronary artery disease, has limited our ability to draw precise conclusions about coronary artery remodeling. Similarly, we did not quantify plaque volume, or total plaque burden, which may be important factors in the remodeling process. Also, we used the known duration of therapy for diabetes as a marker for disease duration, but diabetes may be present for years before the actual diagnosis and treatment. Furthermore, it may be difficult to distinguish between the effects of diabetes duration, the degree of glycemic control, and the need for insulin therapy on the one hand, and the complications of the disease itself on the other. Therefore, the findings of our study may not reflect the different stages of vascular damage in the diabetic subjects, but instead reflect the effects of advanced diabetes.

References