Impact of type 2 diabetes on serial changes in tissue characteristics of coronary plaques: an integrated backscatter intravascular ultrasound analysis

Shinji Inaba1, Hideki Okayama2*, Jun-ichi Funada3, Haruhiko Higashi4, Makoto Saito4, Toyofumi Yoshii4, Go Hiasa4, Takumi Sumimoto4, Yasunori Takata5, Kazuhisa Nishimura1, Katsuji Inoue1, Akiyoshi Ogimoto1, and Jitsuo Higaki1

1Division of Cardiology, Department of Integrated Medicine and Informatics, Ehime University Graduate School of Medicine, Toon, Ehime, Japan; 2Department of Cardiology, Ehime Prefectural Central Hospital, Kasuga, Matsuyama, Ehime 790-0024, Japan; 3Department of Cardiology, Ehime National Hospital, Toon, Ehime, Japan; 4Department of Cardiology, Kitaishikai Hospital, Ozu, Ehime, Japan; and 5Department of Molecular and Genetic Medicine, Ehime University Graduate School of Medicine, Toon, Ehime, Japan

Received 28 November 2011; accepted after revision 30 January 2012; online publish-ahead-of-print 24 February 2012

Aims

Several studies have demonstrated that type 2 diabetes mellitus (T2DM) is associated with accelerated atherosclerosis, which results in an increased risk of coronary vascular events. However, serial changes in plaque characteristics have not been reported in vivo. We evaluated the progression of coronary atherosclerosis in patients with T2DM using an integrated backscatter intravascular ultrasound (IB-IVUS) examination.

Methods and results

Forty-two T2DM and 48 non-diabetic patients who underwent percutaneous coronary intervention were enrolled in the study. Non-culprit 20-mm length coronary lesions with mild-to-moderate stenosis were measured using a 40-MHz (motorized pullback of 0.5 mm/s) IVUS catheter. IVUS examinations were performed on one target lesion in each patient. Six months later, a follow-up IVUS examination was repeated in the same coronary segment imaged at the baseline examination. T2DM patients demonstrated a greater total plaque volume (TPV; $139 \pm 53$ vs. $114 \pm 45$ mm$^3$, $P = 0.02$) and total lipid volume (TLV; $67 \pm 26$ vs. $55 \pm 30$ mm$^3$, $P = 0.039$) at the baseline examination. The progression of TPV ($8.6 \pm 15.4$ vs. $22.2 \pm 20.0\%$, $P < 0.01$) and TLV ($10.8 \pm 28.8$ vs. $2.5 \pm 0.0$) from the baseline was observed in T2DM patients, but not in non-diabetic patients. The increase in TLV was blunted in T2DM patients who achieved HbA1c levels of $< 6.5\%$.

Conclusion

Accelerated plaque progression with an increase in the lipid-rich component of non-culprit plaques was observed in T2DM, despite the use of standard medical treatment. Better glycaemic control ameliorated the worsening of plaque characteristics in T2DM.

Keywords

Type 2 diabetes • Integrated backscatter intravascular ultrasound • Lipid-rich plaque • Coronary artery disease

Introduction

The number of patients with diabetes mellitus has reached ~285 million worldwide and is increasing every year. Diabetes and its systemic complications have become an excessive medical and economic burden in the world. Among many complications in diabetes, the prevalence of cardiovascular events is high, and thus prevention of these events is crucial. Recent randomized controlled trials have failed to prove a favourable effect of intensive glycaemic control on secondary cardiovascular prevention. It has been reported that the duration of diabetes and hypoglycaemia seems to affect adverse outcomes. In contrast, the UKPDS 80 and Steno-2 studies, which employed comprehensive treatment of type 2 diabetes mellitus (T2DM) at an early stage, showed...
reduced cardiovascular mortality.\textsuperscript{6,7} Taken together, early intensive intervention without hypoglycaemia appears to ameliorate cardiovascular events. However, there has been a lack of evidence that links changes in the tissue components of atheromatous plaques and glycaemic control status.

Intravascular ultrasound (IVUS) has been used for the evaluation of coronary atherosclerosis burden in various diseases and during serial drug interventions with statins, calcium channel blockers or pioglitazone.\textsuperscript{8–10} Analysis of pooled data from several IVUS studies has shown that diabetic coronary arteries have characteristic vessel remodelling compared with non-diabetic coronaries.\textsuperscript{11,12} However, grey-scale IVUS can analyse the plaque volume but not the tissue characteristics of coronary plaques. Integrated backscatter IVUS (IB-IVUS) developed by Kawasaki et al.\textsuperscript{13–15} can identify coronary atheroma components such as lipid, fibrous, dense fibrous and calcification with high sensitivity and specificity in comparison with histology. Accordingly, we hypothesized that plaque characteristic in T2DM patients during the follow-up could be altered compared with non-diabetics and affected by the degree of glycaemic control. In this study, we aimed to clarify serial changes of plaque characteristics using IB-IVUS in patients with T2DM.

**Methods**

**Patients and study design**

The study enrolled 100 consecutive patients with coronary artery disease who underwent percutaneous coronary intervention (PCI) in the culprit lesions. Ten patients were excluded from the analysis because of poor IVUS quality and 90 patients with unstable angina pectoris (UAP) or stable angina pectoris (SAP) were included in the final analysis. According to the criteria of the American Diabetic Association for T2DM, patients were divided into a group of 42 with T2DM and a group of 48 without diabetes.\textsuperscript{16} Exclusion criteria were acute myocardial infarction, left main coronary artery disease, lesions with chronic total occlusion, patients receiving haemodialysis, type 1 diabetes mellitus, and prior coronary artery bypass graft surgery. In addition, we excluded diabetic patients receiving insulin treatment, because several studies demonstrated that the plaque progression pattern in patients treated with insulin differs from those treated with oral antidiabetic medications.\textsuperscript{11} UAP was defined as either as new-onset angina within 2 months after a previous bout, angina with a progressive crescendo pattern (with anginal episodes increasing in frequency or duration) or angina that occurred at rest. SAP was defined as the chest pain typical of cardiac ischaemia on exertion. The study was approved by the ethics committee at our hospital and informed consent was obtained from all patients before the study.

**IVUS imaging**

Candidate plaques were required to demonstrate <50% diameter stenosis by angiographic measurement. After administration of 0.5 mg of intracoronary isosorbide dinitrate, IVUS images were obtained from a 20-mm length of vessel that had a non-culprit lesion using a 40-MHz IVUS catheter (Atlantis\textsuperscript{TM} SR Pro\textsuperscript{2}, Boston Scientific, Natick, MA, USA). The catheter was attached to an IVUS imaging system (Galaxy\textsuperscript{17}, Boston Scientific, Natick, MA, USA) with motorized pullback at 0.5-mm/s. The operators made effort to ensure that a measured segment included definable side branches to ensure a reliable comparison between the baseline and follow-up examinations.

Corresponding images were identified by the distance from fiduciary side branches. IVUS examinations were performed on one target lesion in each patient. Accordingly, a total of 90 non-culprit plaques (42 in T2DM and 48 in non-diabetics) were examined in this study. IB-IVUS images were obtained using a personal computer equipped with custom software (IB-IVUS, YD Co., Ltd., Nara, Japan) that acquired the radio frequency signal output, signal trigger output and video image output of the IVUS imaging system. IB values for each histological category were determined by previous IB-IVUS studies.\textsuperscript{15,17} Six months later, a follow-up IVUS examination was repeated in the same coronary segment imaged at the baseline examination.

**Measurements of conventional and IB-IVUS parameters**

Each conventional IVUS and IB-IVUS parameter was measured at baseline and after 6 months in each group. One experienced investigator who was unaware of the patient group allocation performed the quantitative IVUS analysis. In the conventional IVUS analyses, external elastic membrane (EEM) cross-sectional area (CSA) and lumen CSA were traced manually at each site using software supplied with the IVUS machine. Plaque CSA was defined as EEM CSA minus lumen CSA. Then, the total vessel volume, total lumen volume, and total plaque volume (TPV) were calculated by Simpson’s method as previously described.\textsuperscript{18} The plaque burden (%) was calculated as the TPV/total vessel volume × 100. The percentage of lipid area and the percentage of fibrous area at each slice were automatically calculated by the IB-IVUS system. The total lipid volume (TLV) and total fibrous volume (TFV) were also calculated by Simpson’s method. The percentage of TLV and the percentage of TFV were calculated according to the following formula: TLV/TPV × 100, TFV/TPV × 100. The per cent change in each volume was calculated as: (volume at follow-up – volume at baseline)/volume at baseline × 100.

**Statistical analysis**

Statistical analysis was carried out using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). Results are expressed as the mean ± SD for continuous variables and as percentage for categorical variables. Differences between the two groups with and without diabetes were assessed with a χ\textsuperscript{2} test for categorical variables and with an unpaired Student’s t-test for continuous variables. Correlations between per cent change in TLV and glycated haemoglobin at follow-up were analysed by linear regression analysis. Multiple regression analysis was performed to identify the independent predictors of % change of TLV. A value of P < 0.05 was considered to indicate statistical significance.

**Results**

**Clinical characteristics**

Baseline clinical characteristics in patients with and without diabetes are summarized in Table 1. There were no significant differences between the two groups, excluding body mass index. The coronary risk factors at the baseline and follow-up examinations are summarized in Table 2. Diabetic patients had higher levels of fasting glucose and glycated haemoglobin at the baseline. In non-diabetic subjects, there was no significant change in the level of glycated haemoglobin. In contrast, the level of glycated haemoglobin decreased significantly in diabetic patients who received standard medical treatment during the course of the study (P < 0.05).
Quantitative parameters of conventional and IB-IVUS

Table 3 shows measures of conventional and IB-IVUS parameters at the baseline and follow-up examinations in patients with and without T2DM. In conventional IVUS analysis, there were no significant differences in the total vessel volume and the total lumen volume between the two groups. However, the TPV, and the plaque burden were significantly greater in diabetic subjects even at the baseline examination. Moreover, the TLV was significantly greater in diabetic subjects at the baseline in the IB-IVUS analysis. TLV in diabetic subjects further increased at the follow-up examination.

TPV and TLV in non-diabetic subjects showed no significant changes during 6 months follow-up. However, TPV and TLV in diabetic subjects significantly increased. Serial changes in conventional and IB-IVUS profiles are summarized in Figure 1. The % change in TPV (8.6 ± 15.4%) in diabetic subjects was significantly greater than that in non-diabetic subjects (−2.2 ± 16.0%, P < 0.01). Furthermore, in IB-IVUS, the % change in TLV (10.8 ± 28.8%) in diabetic subjects was significantly higher than that in non-diabetic subjects (−2.5 ± 20.0%, P < 0.05). In contrast, there was no significant difference in the % change in TFV between the two groups. Multivariate regression analysis after adjustment for potentially confounding risk factors showed that the glycated haemoglobin level at the follow-up examination remains correlated independently with the % change in TLV (Table 4).

Association of glycaemic control with plaque progression in patients with diabetes

Figure 2 shows the relationship between glycaemic control and plaque progression in diabetic subjects. The glycated haemoglobin level at the follow-up examination was significantly correlated with the % change in TFV (Figure 2A). Figure 2B shows plaque progression according to glycaemic control. The % change TLV (−3.3 ± 22.5 vs. 26.2 ± 27.3%, P < 0.001) was significantly lower in diabetic subjects who achieved fair glycaemic control (HbA1c < 6.5%) than in those with poor glycaemic control (HbA1c ≥ 6.5%). On the other hand, the % change TPV (4.9 ± 12.3 vs. 12.6 ± 17.7%, P = 0.11) showed no significant differences between the two
groups. Representative cases from each group are shown in Figure 3.

Reproducibility of data
We examined the intra- and interobserver variability of the TPV, TLV, and TFV in 10 randomly selected recordings. Intraobserver variabilities of each volume were $3.4 \pm 1.6\%$, $3.7 \pm 2.3\%$, and $3.9 \pm 2.0\%$. Interobserver variabilities of each volume were $2.8 \pm 1.9\%$, $4.0 \pm 2.4\%$, and $3.9 \pm 2.4\%$.

Discussion
The major findings of this study were as follows: (i) the accelerated plaque progression was observed in patients with T2DM on a grey-scale IVUS analysis, (ii) a lipid-rich component of a non-culprit plaque in T2DM during the follow-up was increased on IB-IVUS analysis, and (iii) a better glycaemic status may have a preventive effect on the worsening of plaque characteristics in T2DM patients.

Atheroma progression in T2DM
In this study, the plaque burden was significantly higher in patients with T2DM than without T2DM, even at the baseline. Moreover, the plaque burden in T2DM patients further increased during the follow-up. Nicholls et al. have shown from pooled IVUS data that coronary atherosclerosis progression in diabetic subjects was exaggerated, and their results support our findings. However, in this previous study, atheroma progression was reduced with aggressive lowering of low-density lipoprotein (LDL) cholesterol ($<80$ mg/dl) in diabetic subjects. Intensive lowering of LDL cholesterol might have reduced atheroma progression in the present study, because the mean value of LDL cholesterol in T2DM patients was $\sim 100$ mg/dL at the 6-month follow-up. It has been also reported that intensive statin therapy could reduce the non-culprit coronary plaque volume. In the present study, we failed to perform the strict lipid monitoring after discharge to verify whether the lowering of target lipid was

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Measures of conventional and IB-IVUS parameters at baseline and follow-up in patients with and without diabetes</th>
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<tbody>
<tr>
<td>Parameter</td>
<td>Non-diabetic ($n = 48$)</td>
</tr>
<tr>
<td>Conventional IVUS</td>
<td></td>
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<tr>
<td>Total vessel volume (mm$^3$)</td>
<td>Baseline 280 ± 91</td>
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<tr>
<td></td>
<td>Follow-up 272 ± 87</td>
</tr>
<tr>
<td>Total lumen volume (mm$^3$)</td>
<td>Baseline 166 ± 62</td>
</tr>
<tr>
<td></td>
<td>Follow-up 162 ± 60</td>
</tr>
<tr>
<td>TPV (mm$^3$)</td>
<td>Baseline 114 ± 45</td>
</tr>
<tr>
<td></td>
<td>Follow-up 110 ± 42</td>
</tr>
<tr>
<td>Plaque burden (%)</td>
<td>Baseline 41 ± 10</td>
</tr>
<tr>
<td></td>
<td>Follow-up 41 ± 10</td>
</tr>
<tr>
<td>IB-IVUS</td>
<td></td>
</tr>
<tr>
<td>TLV (mm$^3$)</td>
<td>Baseline 55 ± 30</td>
</tr>
<tr>
<td></td>
<td>Follow-up 53 ± 29</td>
</tr>
<tr>
<td>Per cent lipid volume (%)</td>
<td>Baseline 46 ± 10</td>
</tr>
<tr>
<td></td>
<td>Follow-up 46 ± 12</td>
</tr>
<tr>
<td>TFV (mm$^3$)</td>
<td>Baseline 51 ± 17</td>
</tr>
<tr>
<td></td>
<td>Follow-up 50 ± 19</td>
</tr>
<tr>
<td>Per cent fibrous volume (%)</td>
<td>Baseline 47 ± 9</td>
</tr>
<tr>
<td></td>
<td>Follow-up 47 ± 10</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

IVUS, intravascular ultrasound system; IB, integrated backscatter.

Figure 1  Per cent change in conventional and IB-IVUS profiles during the 6-month follow-up. A significant increase in the plaque volume and lipid volume was observed in patients with T2DM compared with non-diabetic subjects.
achieved. Kawasaki et al.17 previously reported using IB-IVUS that statin therapy reduce the lipid-rich component without reducing the plaque volume. Therefore, adequate statin therapy might have a greater potential for plaque stability rather than reduction. However, it is not fully understood whether intensive statin therapy might be effective on plaque stabilization even in T2DM. To clarify the issue, further investigations are needed. Furthermore, the PERISCOPE study showed that an insulin sensitizer, pioglitazone, can reduce the progression of coronary atherosclerosis in patients with T2DM using the grey-scale IVUS.10 The preventive effect on coronary atherosclerosis might differ among various anti-diabetic drugs. Moreover, the effect of pioglitazone or other anti-diabetic drugs on tissue characteristics of coronary plaques in T2DM remains unclear. Further studies are needed to evaluate the effects of various anti-diabetic drugs on both plaque characteristics and plaque progression.

### Impact of T2DM on tissue characteristics

Histopathological studies have demonstrated that T2DM is associated with a greater macrophage infiltration and large necrotic core, which may result in an increased risk of cardiovascular events.19–21 Amano et al.22 have reported that abnormal glucose regulation is associated with increased lipid-rich plaque using IB-IVUS. Nasu et al.23 also have shown an increased necrotic core of culprit lesions in T2DM patients compared with non-diabetics using virtual histology IVUS. Their results suggest that T2DM causes accelerated atherosclerosis compared with non-diabetic subjects, and this is consistent with our observations of non-culprit lesions. However, there has been no report of serial changes in plaque characteristics in T2DM. The present longitudinal study clearly demonstrated that the lipid-rich component as well as the plaque burden in non-culprit coronary plaques was exaggerated in patients with T2DM. Recent pooled IVUS data analysis has shown that a direct relationship was observed between the burden of coronary atherosclerosis, its progression, and adverse cardiovascular events.24 Sano et al. have demonstrated that an increase in the % lipid volume of coronary plaques is associated with an increase in the future incidence of acute coronary syndrome.25 Thus, our results suggest that there is greater plaque instability in T2DM, resulting in a higher incidence of cardiovascular events.

### Glycaemic status and plaque characteristics

It is not clear whether improving glycaemic status improves clinical outcomes. Three recently published randomized controlled trials (ACCORD, ADVANCE, and VADT) did not find a significant reduction in cardiovascular events with intensive treatment compared with standard treatment of T2DM.2–4 Furthermore, the ACCORD study showed that intensive glycaemic control is

<table>
<thead>
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<th>Variable</th>
<th>Beta coefficient</th>
<th>t</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>-0.04</td>
<td>-0.44</td>
<td>0.66</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-0.02</td>
<td>-0.24</td>
<td>0.81</td>
</tr>
<tr>
<td>UAP</td>
<td>-0.18</td>
<td>-1.95</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean BP at follow-up</td>
<td>0.11</td>
<td>1.10</td>
<td>0.27</td>
</tr>
<tr>
<td>Statin</td>
<td>-0.05</td>
<td>-0.46</td>
<td>0.65</td>
</tr>
<tr>
<td>HbA1c at follow-up</td>
<td>0.43</td>
<td>4.49</td>
<td>&lt;0.001</td>
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</table>

Covariates: age, gender, unstable angina pectoris, mean blood pressure at follow-up, statin use, and HbA1c at follow-up. UAP, unstable angina pectoris; BP, blood pressure. $R^2 = 0.19; P < 0.001$ for the model.
harmful in terms of overall mortality and cardiovascular mortality. Thus, the target goal of glycaemic control remains unclear. The recent glycaemic goal recommended by the American Diabetes Association/the American Heart Association is an HbA1c level of <7.0%.26 In contrast, the recent glycaemic goal set by the International Diabetes Foundation is an HbA1c level of <6.5%.26 We demonstrated a positive correlation between HbA1c at follow-up and the % change in TLV in coronary plaques in T2DM patients. Moreover, an increase in the lipid-rich component was more advanced in T2DM patients with poor glycaemic control than in T2DM patients with fair glycaemic control. Thus, our observations suggest that adequate glycaemic control ameliorated the worsening of plaque characteristics in T2DM, which may reduce the incidence of subsequent cardiovascular events.

Study limitations

This study has several limitations. First, the thin-cap fibroatheroma, which is considered to be one of the predominant markers of vulnerable plaque, cannot be accurately measured by IB-IVUS because of inadequate spatial resolution. To further clarify the link between accelerated plaque progression in T2DM and plaque vulnerability or incidence of cardiovascular events, studies using other modalities (i.e. optical coherence tomography) are needed. In addition, a serial intravascular ultrasound assessment has potential limitations such as matching of baseline and follow-up lesions, non-uniform rotational distortion or a difference in ultrasound intensity due to the IVUS catheter position.27 Furthermore, the present study was performed in T2DM patients who underwent PCI. Patients who were indicated for coronary artery bypass graft surgery (i.e. diffuse or multivessel disease) were excluded from the study, as well as patients who had lesions that were not suitable for IVUS analysis (i.e. heavily calcified or small vessels). Therefore, serial changes in more advanced diabetic coronary atherosclerosis remain unclear. Finally, HbA1c was analysed only at follow-up. Monthly measurements during the follow-up period are needed to more accurately evaluate the relationship between glycaemic control and the IB-IVUS findings.

Conclusions

Our serial IVUS assessments revealed that plaque progression in patients with T2DM is enhanced with an increase in the lipid-rich component during 6 months of follow-up. Better glycaemic control may prevent the worsening of plaque characteristics and reduce subsequent cardiovascular events.

Conflict of interest: none declared.

Funding

None.

References


