Plasma Glucagon-Like Peptide-1 and Tissue Characteristics of Coronary Plaque in Non-Diabetic Acute Coronary Syndrome Patients

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Background: The relationship between plasma glucagon-like peptide-1 (GLP-1) and coronary plaque characteristics in humans remains unclear.

Methods and Results: A total of 85 culprit coronary vessels excluding the 10-mm culprit segments in non-diabetic patients with acute coronary syndrome (ACS) were examined using integrated backscatter intravascular ultrasound, performed using a 40-MHz intravascular catheter before PCI. All patients underwent 75-g oral glucose tolerance test (OGTT), and the plasma GLP-1 response was evaluated on the basis of the area under the GLP-1 concentration-time curve (GLP-1 AUC) from 0 to 120 min. Patients in the low GLP-1 AUC tertile had a significantly greater percentage lipid area than did patients in the intermediate and high tertiles (low tertile vs. intermediate tertile vs. high tertile: 57.3±12.1% vs. 47.2±15.4% vs. 46.3±12.7%, P<0.01, ANOVA) and a smaller percentage fibrosis area (38.1±9.4% vs. 44.6±11.5% vs. 45.7±9.0%; P=0.01, ANOVA). On multiple regression analysis, low GLP-1 AUC tertile was independently associated with percentage lipid area.

Conclusions: Low plasma GLP-1 during 75-g OGTT is associated with increased lipid content in non-diabetic patients with ACS, suggesting that plaque vulnerability is increased in this subgroup of patients. (Circ J 2016; 80: 469 – 476)

Key Words: Glucagon-like peptide-1; Intravascular ultrasound; Vulnerable plaque

Type 2 diabetes mellitus (T2DM) is a well-known risk factor for coronary artery disease (CAD). Accumulated evidence indicates that coronary atherosclerosis is accelerated not only in diabetic patients, but also in prediabetic patients with abnormal glucose metabolism (AGM), as compared with individuals who have normal glucose metabolism. Therefore, a better understanding of the mechanisms linking AGM to CAD is needed to develop new strategies to prevent premature mortality from cardiovascular disease in patients with AGM.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that is secreted from intestinal L-cells in response to nutritional stimuli leading to pancreatic insulin secretion and suppression of glucagon release. GLP-1 inhibits gastric motility and reduces appetite, which in conjunction improve postprandial glucose metabolism. In addition, GLP-1 has vasoprotective effects. Previous studies have reported that GLP-1 is decreased in patients with T2DM. GLP-1-based therapies, such as GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase 4 (DPP-4), have been established to effectively lower glucose level and are frequently used to treat patients with T2DM. Matsubara et al noted a significant inverse correlation between plasma GLP-1 and the area of atherosclerosis lesions in apolipoprotein E-deficient mice, indicating an anti-atherosclerotic effect of GLP-1. A recent meta-analysis of clinical trial data showed that DPP-4 inhibitors are associated with a lower risk of major cardiovascular events as compared with other classes of anti-diabetic agents.

Kawasaki et al have developed a technique for integrated backscatter intravascular ultrasound (IB-IVUS) that can identify different components of atherosclerotic plaque in human coronary arteries in vivo. They also showed that lipid-rich plaque causes subsequent acute coronary syndromes (ACS). Thus, IB-IVUS seems to be the useful for identifying
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coronary plaque in patients with ACS. Consecutive patients with ACS who underwent percutaneous coronary intervention (PCI) with IVUS guidance at Yokohama City University Medical Center were screened for eligibility. Patients with a previous diagnosis of DM and HbA1c >6.5% were excluded. A total of 115 patients in stable condition underwent 75-g oral glucose tolerance test (OGTT) before hospital discharge. We excluded 26 patients in whom DM was diagnosed on OGTT and 4 patients for whom IB-IVUS data were unavailable. Finally, 85 culprit vessels in 85 non-diabetic patients with ACS were studied. The study protocol was approved by the ethics committee of Yokohama City University Medical Center. We obtained written informed consent from all participants before initial coronary angiography.

Cardiovascular Diagnosis
ACS was defined as unstable angina, ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction (NSTEMI). Unstable angina was defined as new-onset severe angina, accelerated angina, or angina at rest without a significant rise in cardiac-specific troponin T. New-onset angina was defined as angina in which <2 months had elapsed from the date of initial symptoms. Accelerated angina was defined as angina in which symptoms were more frequent, severer, longer, or precipitated by distinctively less exertion than previously, while the patient was in stable condition. STEMI was defined as the continuous presence of chest symptoms >30 min, ST-segment elevation >0.1 mV in 2 limb leads or >0.2 mV in 2 contiguous precordial leads, and a rise in cardiac-specific troponin T. NSTEMI was defined as chest pain and a rise in cardiac-specific troponin T without new ST-segment elevation.

Glucose Metabolism and Lipid Profile
Patients without a prior diagnosis of DM underwent 75-g OGTT while they were in stable condition at least 4 days after admission. After overnight fast, venous blood samples for the measurement of plasma glucose, plasma insulin, and plasma GLP-1(7-36) amide, the active form of GLP-1, were taken at baseline and 30, 60, and 120 min after glucose load. Glucose metabolism was then classified according to the results of OGTT as follows: impaired glucose tolerance (IGT), fasting blood glucose <126 mg/dl and 120-min post-load blood glucose ≥140 mg/dl, but <200 mg/dl; DM, fasting blood glucose ≥126 mg/dl or 120-min post-load blood glucose ≥200 mg/dl.

The area under the plasma GLP-1 concentration-time curve (GLP-1 AUC) was calculated from plasma GLP-1 at baseline, 30, 60, and 120 min after glucose load. GLP-1 AUC was used as a composite variable reflecting plasma GLP-1 level.

Various serum markers, including lipid profiles, were measured with the use of commercial radioimmunoassay kits. For this purpose, blood samples were collected at admission.

IVUS and IB-IVUS
Culprit vessels were identified by comprehensively evaluating electrocardiographic findings, left ventricle wall abnormalities (left ventriculography or echocardiography), and angiographic lesion morphology. We excluded patients with multivessel coronary disease if the culprit lesion was not identified. IVUS was performed, using a 40-MHz mechanical scanning monorail intracoronary ultrasound catheter (Atlantis Pro; Boston Scientific, Natick, MA, USA; or ViewIT™; Terumo, Tokyo, Japan) before balloon dilatation or stent implantation. Thrombus aspiration was performed prior to IVUS as necessary. IVUS vulnerable plaque.

The aim of this study was to ascertain whether plasma GLP-1 is associated with the tissue characteristics of culprit coronary plaques in patients with ACS.

Methods
Subjects
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vulnerable plaque.

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Figure 1. Glucagon-like peptide-1 (GLP-1) secretion and blood glucose and insulin levels in response to 75-g oral glucose tolerance test (OGTT). Plasma GLP-1 peaked at 30 min in both the normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) groups and decreased at 60 and 120 min. Plasma GLP-1 at 30, 60, and 120 min tended to be lower in patients with IGT than in those with NGT.
was performed in the following manner. After intracoronary isosorbide dinitrate 2–3 mg, the catheter was advanced sufficiently distal in the culprit vessels. Pullback was performed automatically at 0.5 nm/s. All IVUS imaging data were stored in the console. The data were quantitatively analyzed with a software system (IB-IVUS, YD, Nara, Japan or VISIATLAS TM, Terumo). The IB-IVUS technology has been described in detail elsewhere.\textsuperscript{15} Tissue composition of coronary plaque was classified into the following 4 types according to the radiofrequency ultrasound backscatter signals: lipid; fibrosis; dense fibrosis; and calcification. Ohota et al noted a close agreement between the histological characteristics of major plaque constituents and the clinical characteristics evaluated with Boston Scientific and Terumo IVUS catheters.\textsuperscript{16} We have previously reported good intraobserver and interobserver agreement for the measurement of coronary plaque components.\textsuperscript{17}

**Conventional IVUS and IB-IVUS Data**

On grayscale IVUS and IB-IVUS analysis, we evaluated the culprit vessels at 1-mm intervals excluding the 10-mm length segment centered at the minimum lumen area (MLA) site. Quantitative analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on IVUS.\textsuperscript{18} The cross-sectional area (CSA) measurements included the lumen and the external elastic membrane (EEM) CSA. The lumen-intima border was traced manually to determine the lumen CSA. EEM CSA was measured by tracing the external edge of the media-adventitia border. Plaque plus media (P+M) CSA was calculated as the EEM CSA minus the lumen CSA. EEM, lumen, and P+M volumes were calculated using Simpson’s method for the integration of 1-mm-thick disks. To compensate for differences in analyzed length among subjects, normalized EEM or lumen or P+M volume were defined as \([\text{EEM or lumen or P+M volume} \times \text{mean analyzed length in study population}]\].

Percent P+M volume was calculated as the percentage of EEM volume that was occupied by total P+M volume.

Color-coded maps based on IB values were constructed for consecutive IVUS image slices of the target plaque. Because the media of the coronary arteries always presents with a low echoic band, potentially identified as “lipid” by the algorithm currently used for IB-IVUS, the lumen-intima border and intima-media border were traced manually. Additionally, we excluded guidewire artifact area from analysis. The average value of each plaque component was expressed relative to the total volume.

### Table 1. Baseline Patient Clinical Characteristics vs. GLP-1 AUC Tertile

<table>
<thead>
<tr>
<th></th>
<th>Low tertile (n=29)</th>
<th>Intermediate tertile (n=27)</th>
<th>High tertile (n=28)</th>
<th>P-value*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58±10*††</td>
<td>64±13</td>
<td>70±7*††</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male</td>
<td>26 (90)</td>
<td>24 (86)</td>
<td>19 (68)</td>
<td>0.08</td>
</tr>
<tr>
<td>Target plaque location</td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>13 (45)</td>
<td>17 (61)</td>
<td>13 (46)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>6 (21)</td>
<td>2 (7)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>10 (35)</td>
<td>9 (32)</td>
<td>12 (43)</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3 (10)</td>
<td>3 (11)</td>
<td>4 (14)</td>
<td></td>
</tr>
<tr>
<td>Non-ST elevation MI</td>
<td>4 (14)</td>
<td>3 (11)</td>
<td>6 (21)</td>
<td></td>
</tr>
<tr>
<td>ST elevation MI</td>
<td>22 (76)</td>
<td>22 (79)</td>
<td>18 (64)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>13 (45)</td>
<td>11 (39)</td>
<td>11 (39)</td>
<td>0.89</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.9±3.0</td>
<td>24.1±4.0</td>
<td>22.3±2.7*††</td>
<td>0.01</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87±8</td>
<td>86±9</td>
<td>84±9</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (79)</td>
<td>21 (74)</td>
<td>18 (64)</td>
<td>0.45</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18 (62)</td>
<td>16 (57)</td>
<td>12 (43)</td>
<td>0.33</td>
</tr>
<tr>
<td>Blood lipid level (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>150±36</td>
<td>136±29</td>
<td>120±31*†</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C</td>
<td>46±12</td>
<td>48±13</td>
<td>47±12</td>
<td>0.91</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>131 (87–171)</td>
<td>152 (76–186)</td>
<td>127 (62–186)</td>
<td>0.54</td>
</tr>
<tr>
<td>Statin use at admission</td>
<td>5 (17)</td>
<td>4 (14)</td>
<td>6 (21)</td>
<td>0.79</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.545 (0.067–0.471)</td>
<td>0.329 (0.084–0.372)</td>
<td>0.647 (0.058–0.386)</td>
<td>0.50</td>
</tr>
<tr>
<td>IG T</td>
<td>20 (69)</td>
<td>18 (64)</td>
<td>13 (46)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.4±0.5</td>
<td>5.5±0.3</td>
<td>5.6±0.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>100±7</td>
<td>98±7</td>
<td>100±9</td>
<td>0.70</td>
</tr>
<tr>
<td>Fasting insulin (IU/L)</td>
<td>8.9±3.1</td>
<td>8.3±4.7</td>
<td>5.8±2.9*††</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting GLP-1 (pmol/L)</td>
<td>0.9±1.3*†‡</td>
<td>2.0±1.5</td>
<td>2.3±2.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GLP-1 AUC (pmol/L•min)</td>
<td>290±84</td>
<td>493±73</td>
<td>1,668±1,229*†‡</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data given as mean±SD, median (IQR) or n (%). *P<0.05 †vs. low tertile and intermediate tertile; ‡vs. intermediate tertile and high tertile; †vs. low tertile; §vs. intermediate tertile. *Chi-squared test, analysis of variance, or Kruskal-Wallis test among the 3 tertiles. GLP-1 AUC, area under the glucagon-like peptide-1 concentration-time curve; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IG T, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.
coefficients were calculated. Differences with P<0.05 were considered statistically significant.

**Results**

**GLP-1 Secretion in Response to 75-g OGTT**

The mean interval between the onset of ACS and 75-g OGTT was 12.8±10.3 days. Figure 1 shows the time course of plasma GLP-1 in response to a 75-g OGTT. After oral glucose, plasma GLP-1 peaked at 30 min in both the normal glucose tolerance (NGT) and IGT groups. At 60 min, plasma GLP-1 decreased, but remained higher than the fasting GLP-1 for up to 120 min. GLP-1 tended to be lower in patients with IGT than in those with NGT at 30 min (8.3±4.5 pmol/L vs. 12.6±8.6 pmol/L, P<0.01), ANOVA), as well as a significantly lower percentage fibrosis area (38.1±8.9% vs. 44.6±11.5% vs. 45.7±9.0%, P<0.01, ANOVA).

**Subjects and Baseline Characteristics**

Mean patient age was 64±11 years. Eighty-one percent of the

### Statistical Analysis

Statistical analysis was performed using StatView 5.0 (SAS Institute, Cary, NC, USA). Qualitative data are presented as n (%). Normally distributed, continuous variables are expressed as mean±SD, and continuous variables with skewed distributions (triglycerides and C-reactive protein) are expressed as median (IQR). Categorical variables were compared using the chi-squared test. Continuous clinical and IVUS variables were compared among the 3 groups on ANOVA. Correlations of plaque contents, as assessed on IB-IVUS, with low GLP-1 AUC tertile and clinical and laboratory variables were evaluated using simple regression analysis. Multiple linear regression analysis was used to determine the best predictors of percentage lipid area. Logarithms (base 2) of triglycerides and C-reactive protein were used in all regression analyses to account for the skewed distributions of these variables. Univariate predictors of percentage lipid area with P<0.2 were entered into the multivariate model. Independent predictors and their regression coefficients were calculated. Differences with P<0.05 were considered statistically significant.

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significantly lower in the low GLP-1 AUC tertile than in the other tertiles. IVUS and IB-IVUS: Quantitative Measurement

Table 2 lists the results of conventional grayscale IVUS analyses. Normalized EEM, lumen, and P+M volumes were similar in the 3 groups.

On IB-IVUS analysis, patients in the low GLP-1 AUC tertile had a significantly greater percentage lipid area than those in the intermediate and high tertiles (57.3 ± 15.4% vs. 46.3 ± 12.7%, P < 0.01, ANOVA), as well as a smaller percentage fibrosis area (38.1 ± 9.4% vs. 44.6 ± 11.5% vs. 45.7 ± 9.0%, P < 0.01, ANOVA; Figure 2). Figure 3 shows representative conventional IVUS images and IB-IVUS color-coded maps of a non-culprit coronary plaque in patients in the low and high GLP-1 AUC tertiles.

Indicators of Percentage Lipid Area

The low GLP-1 AUC tertile was included in simple and multiple regression analysis with percentage lipid area as the dependent variable because low GLP-1 AUC tertile was associated with a significantly greater percentage lipid area as compared with the intermediate and high tertiles (P < 0.05, respectively). On simple regression analysis, low GLP-1 AUC tertile (r = 0.36, P < 0.01) and LDL-C (r = 0.22, P = 0.04) correlated significantly lower in the low GLP-1 AUC tertile than in the other tertiles.

Figure 3. Representative conventional intravascular ultrasound (IVUS) images and integrated backscatter IVUS (IB-IVUS) color-coded maps of coronary artery plaques in a patient in the low area under the glucagon-like peptide-1 concentration-time curve (GLP-1 AUC) tertile (Top panels) and in that with high GLP-1 AUC tertile (Bottom panels). Percentage lipid area and fibrosis area of coronary artery plaque were (Top panels) 66.1% and 32.9%, respectively (GLP-1 AUC, 174); and (Bottom panels) 20.4% and 59.3%, respectively (GLP-1 AUC, 2172). Blue, lipid area; green, fibrosis.
Lipid incorporation into the arterial wall is the key event in the initiation of atherosclerosis, and the formation of a soft lipid core is an important determinant of spontaneous plaque rupture. Therefore, IB-IVUS is a well-validated and established method that provides accurate information on tissue characteristics of coronary plaque. We found that low plasma GLP-1 was associated with a significantly increased lipid content of culprit lesions in patients with ACS. These results provide important insights into the relationship between plasma GLP-1 and plaque stability.

Previous studies have reported that disruption of vulnerable plaque and subsequent thrombus formation are the most common causes of ACS. Lipid incorporation into the arterial wall is the key event in the initiation of atherosclerosis, and the formation of a soft lipid core is an important determinant of spontaneous plaque rupture. The PROSPECT study demonstrated that virtual histology IVUS-derived thin-capped fibroatheroma (a fibroatheroma without evidence of a fibrous cap that possessed a >10% confluent necrotic core with a >30° necrotic core abutting the lumen) predicted lesion-specific events during 3 years of follow-up. Several other studies have also demonstrated that tissue characteristics have a great impact on coronary plaque vulnerability. Recent preliminary in vitro studies showed that IB values reflect the structural and biochemical compositions of atherosclerotic lesions and can differentiate fibrofatty, fatty, and calcified lesions of arterial walls. Okubo et al used IB values to analyze lipid-rich, fibrotic, and fibrocalcific coronary plaque components and obtained high predictive accuracies of 90%, 93%, and 96%, respectively, as compared with the corresponding histological images. Therefore, IB-IVUS is a well-validated and established method that provides accurate information on plaque components.

T2DM is a well-recognized major risk factor for CAD. GLP-1 has become a new treatment target for T2DM, with the ultimate goal of reducing the incidence of CAD. A number of studies of GLP-1-based interventions have shown beneficial effects on cardiovascular parameters that might be independent of improved glycemic control. GLP-1 receptor agonists have been shown to reduce body weight and blood pressure in randomized, controlled trials in patients with T2DM. One retrospective analysis showed that an injectable GLP-1 receptor agonist, exenatide, was associated with lower risk of cardiovascular events and hospitalization than was treatment with other glucose-lowering therapies. These findings suggest that GLP-1 might suppress plaque vulnerability. In the present study, low plasma GLP-1 was significantly related to increased plaque lipid content in non-diabetic patients with ACS. The present results are supported by previous experimental as well as human studies, showing that GLP-1 is related to atherosclerotic lesions. Matsubara et al reported a significant inverse correlation between plasma GLP-1 and the area of atherosclerotic lesions in apolipoprotein E-deficient mice. Moreover, they found that fasting active GLP-1 level was significantly lower in patients with CAD than in those without CAD. In addition, Nagashima et al showed that GLP-1 suppressed the formation of atherosclerotic lesions in the aortic wall and decreased foam cell formation in apolipoprotein E-knockout mice. Furthermore, this treatment suppressed acyl-coenzyme A:cholesterol acyltransferase-1, the enzyme that promotes cholesterol ester accumulation, in macrophages. We recently showed that plasma GLP-1 level on admission for acute myocardial infarction is low, and that lower plasma GLP-1 correlates with coronary plaque complexity. These findings suggest that low GLP-1 may be related to lipid-rich atherosclerosis.

Earlier meta-analyses reported that the use of DPP-4 inhibitors was associated with a significant reduction in major adverse cardiovascular events, as compared with placebo or

| Table 3. Significant Correlators With Percentage Lipid Area |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Simple regression |                | Multiple regression |                |                |
|                 | Regression       | P-value         | Regression       | P-value         |                |
| Age             | -0.24            | 0.09            | -0.04            | 0.75            |                |
| Male            | 3.93             | 0.32            | -8.97            | 0.07            |                |
| Body mass index | -0.27            | 0.57            | -8.97            | 0.07            |                |
| Unstable angina | -9.95            | 0.05            | -8.97            | 0.07            |                |
| Non-ST elevation MI | -0.96            | 0.83            | -8.97            | 0.07            |                |
| ST elevation MI | 3.72             | 0.28            | -8.97            | 0.07            |                |
| Hypertension    | -0.88            | 0.80            | -8.97            | 0.07            |                |
| Current smoker  | 2.59             | 0.41            | -8.97            | 0.07            |                |
| LDL-C           | 0.09             | 0.04            | 0.009            | 0.87            |                |
| HDL-C           | -0.06            | 0.62            | -8.97            | 0.07            |                |
| Triglycerides   | -0.008           | 0.66            | -8.97            | 0.07            |                |
| Statin use at admission | -0.81            | 0.84            | -8.97            | 0.07            |                |
| hs-CRP          | 2.03             | 0.18            | 1.92             | 0.18            |                |
| IGT             | 4.63             | 0.14            | 3.58             | 0.24            |                |
| Fasting blood glucose | -0.14           | 0.50            | -8.97            | 0.07            |                |
| Fasting blood insulin | 0.30             | 0.46            | -8.97            | 0.07            |                |
| Low GLP-1 AUC tertile | 10.56          | <0.01           | 9.31             | <0.01           |                |

Abbreviations as in Table 1.
alternative anti-diabetic therapies. Two large cardiovascular outcome trials have been completed, however, and report that the DPP-4 inhibitors saxagliptin and alogliptin do not increase or decrease adverse cardiovascular outcomes in patients with T2DM.\textsuperscript{36,37} There are several potential explanations for the discordance between the meta-analyses and large prospective trials. First, exposure to the study drug may not have been long enough to reverse the long-term effects of pro-atherosclerotic processes in patients with prolonged T2DM. Second, high proportions of patients in previous large cardiovascular outcome trials received statins, antilatelet therapy, and blood pressure-lowering agents, which might have mitigated the cardiovascular risk and blunted potential differences between the study groups. Therefore, properly powered studies with appropriate follow-up and formalized adjudication procedures are needed to provide a full evaluation of the long-term risks and benefits of therapy, and the results of such studies are awaited.

### Study Limitations

Our study had several potential limitations. First, lipid-rich plaque as defined in the present study might not be a major marker of plaque vulnerability. Although previous studies have reported that vulnerable plaque in patients with ACS is related to an increased percentage lipid area,\textsuperscript{11,12,13} large prospective long-term studies are needed to precisely define the value of lipid-rich plaque for predicting future coronary events. Second, this was a single-center study with a relatively small number of patients. Finally, we did not perform 3-vessel IVUS because it is generally considered unacceptable to perform IVUS on non-culprit vessels in the setting of ACS.

### Conclusions

Low plasma GLP-1 during 75-g OGTT was associated with increased lipid content of culprit coronary plaque in patients with ACS without overt T2DM. The evaluation of plasma GLP-1 may help to identify patients at higher risk. Future studies are required to elucidate whether incretin-based therapies can attenuate plaque vulnerability.

### Disclosures / Names of Grant Support

None.

### References

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