Effect of Statin Therapy in Pre-diabetic Status Evaluated by Coronary Angioscopy

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Background: Aggressive lipid-lowering therapy by statins is recommended for the primary and secondary prevention of cardiovascular events in diabetes patients. Although atherosclerotic change has been shown to progress in pre-diabetic patients, the effect of statins in pre-diabetic patients is not well known.

Purpose: To compare the degree of atherosclerosis in pre-diabetic patients with and without statin therapy using coronary angioscopy.

Methods: This was a retrospective cross-sectional study. Twenty-eight pre-diabetic patients underwent angioscopic multi-vessel evaluation of the coronary arteries. The color grade of yellow plaque was defined as 1 (light yellow), 2 (yellow), or 3 (intense yellow) based on semiquantitative analysis of angioscopic findings. The number of yellow plaques (NYP) per vessel and the maximum yellow grade (MYG) were compared between patients with and without statin therapy (statin group and non-statin group, respectively).

Results: Baseline characteristics including serum levels of low-density lipoprotein cholesterol were similar between the two groups. Mean NYP and MYG were significantly lower in the statin group than in the non-statin group (2.03 ± 0.59 vs. 1.12 ± 0.73, P = 0.002; and 2.50 ± 0.71 vs. 1.72 ± 0.83, P = 0.019; respectively).

Conclusions: The coronary angioscopic findings in the present study suggest that statin therapy plays an important role in inhibiting atherosclerotic progression in pre-diabetic patients. From the viewpoint of preventive medicine, statins may be administered in the early stage of glucose metabolism disorder.

Key words: prediabetes, coronary artery disease, yellow plaque, statin, pleiotropic effects

Introduction

Aggressive lipid-lowering therapy by statins is recommended for the primary and secondary prevention of atherosclerotic cardiovascular disease events (ACVD) in diabetes mellitus patients. 1) Diabetes promotes atherosclerotic changes and increases the mortality rate originating from ACVD. 2,3) Nowadays, clinical evidence showing that not only diabetes but also a pre-diabetic status is related to increasing risk of ACVD is accumulating. 4,5) Several investigations using coronary angiogram and intravascular ultrasound elucidate the specific features of advanced coronary atherosclerosis in pre-diabetic patients. 6,7) Previously, coronary angioscopic examination showed that the degree of atherosclerosis in patients with mild glucose metabolism disorder, so called pre-diabetes, is almost equivalent to that in diabetic patients, and pre-diabetic patients are likely to be more vulnerable than individuals with normal glucose metabolism. 8,9)

Lowering of low-density lipoprotein cholesterol (LDL-C) levels by statin therapy induces reduction of the color intensity in yellow plaque, and the phenomenon is regarded as its effect on plaque stabilization. 10) However, it is reported that mature atherosclerotic plaque is composed of a larger necrotic core in diabetes patients, and complete glucose metabolism disorder may attenuate the effect of statins. 11–14)

The effect of statins on coronary plaque in pre-diabetic patients has not been fully validated. The aim of the present study...
was to evaluate the difference in plaque morphology between pre-diabetic patients with and without statin therapy using coronary angioscopy.

Methods

Patient population

Data from 28 pre-diabetic patients who underwent an angioscopic evaluation of plural coronary arteries and successful stenting for the culprit lesion between September 2000 and July 2007 were retrospectively analyzed. Patients were diagnosed as having stable angina pectoris if they had a positive stress test for myocardial ischemia and no change in the frequency, duration, or intensity of clinical symptoms within 4 weeks, including various combinations of chest, upper extremity, jaw, or epigastric discomfort or atypical symptoms (e.g., dyspnea or diaphoresis). Unstable angina pectoris was defined as new-onset severe angina, accelerated angina, or rest angina. Patients who did not have any of the above clinical symptoms were diagnosed as having silent myocardial ischemia. Patients diagnosed as having acute or recent (within 1 month from onset) myocardial infarction during this period were excluded. In addition, coronary arteries with proximal tortuosity, sharp angle, severe calcification, chronic total occlusion, or ostial stenosis were excluded from the analysis because of the expected difficulty in acquiring angioscopic images for the entire vessel. Blood samples were obtained from the antecubital vein in the fasting state before each angioscopic procedure. The baseline diagnosis of glucose metabolism was based on the American Diabetes Association guidelines. Pre-diabetes was defined as a fasting plasma glucose (FPG) concentration of 100–125 mg/dL or a glycated hemoglobin (HbA1c) level of 5.7–6.4% (national glycohemoglobin standardization program, NGSP). The HbA1c value (Japan Diabetes Society +0.4%) was estimated as an NGSP equivalent value calculated using the appropriate formula. Hyperlipidemia was defined as medication-dependent or previously known hyperlipidemia, fasting serum LDL-C >140 mg/dL, or fasting serum total cholesterol >220 mg/dL. The medical ethics committee at Nippon Medical School Chiba Hokusoh Hospital approved the study protocol, and written informed consent was obtained from all patients before the catheterization procedures.

Angioscopic imaging and analysis

The coronary angioscopic procedure has been reported previously. Before observation, the white balance was adjusted for color correction. The light power was adjusted to avoid reflection and to obtain images with adequate brightness for determination of the plaque color. During angioscopic observation, an assistant adjusted the light power to maintain a constant brightness level on the target plaque. Angioscopic images and fluoroscopy during the observations were recorded simultaneously on digital-videotape for later off-line analysis. The yellow grade was classified semi-quantitatively according to the surface color as 0, white; 1, light yellow; 2, yellow; and 3, intense yellow. Yellow plaque was defined simply as a yellow area on the luminal surface. The number of yellow plaques (NYP) was determined for each vessel observed and averaged per vessel. The existence of multiple yellow plaques (MYP) was defined as NYP ≥2 in at least 1 observed vessel. A ruptured plaque was considered to be a wall irregularity, including a tear, flap, or ulceration on the plaque surface. A thrombus was defined as a coalescent red superficial or protruding mass adhering to the vessel surface, but a clearly separate structure that remained after flushing with Ringer lactate.

The angioscopic images were evaluated by an investigator who was blinded to patients’ clinical characteristics. In the previous study performed in our institution, the intra- and inter-observer agreements for evaluated angioscopic items (thrombus, yellow plaque, and complex plaque) were 95%, 100%, and 95%, respectively, and 95%, 98%, and 93%, respectively. The κ values for the intra- and inter-observer agreement of those items were 0.93, 1.00, and 0.88, respectively, and 0.93, 0.95, and 0.84, respectively.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 11.0.1, SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies, and these were compared using the Fisher exact test. Continuous quantitative data are presented as mean value ± SD. All variables were evaluated with the Student t-test. All differences were evaluated at the 95% level of significance (P < 0.05).

Results

Patient characteristics

The clinical characteristics of the 28 patients with pre-diabetes are summarized in Table 1. Eighteen patients were prescribed a statin (statin group; 64%), and 10 patients did not receive statin therapy (non-statin group; 36%). In the statin group, 4 patients (22%), 13 patients (72%), and 1 patient (6%) received pravastatin, atorvastatin, and rosuvastatin therapies, respectively. The average duration of statin intake was 15.8 ± 20.9 months.

Baseline characteristics did not differ between the 2 groups. Mean levels of FPG and HbA1c were similar between the 2 groups (101.1 ± 9.3 mg/dL vs. 103.1 ± 8.7 mg/dL, P = 0.574; 5.8 ± 0.4% vs. 5.6 ± 0.5%, P = 0.318; respectively). Serum C-reactive protein levels were also comparable between the 2 groups.
(0.12 ± 0.10 mg/dL vs. 0.14 ± 0.10 mg/dL, P = 0.575). Although mean levels of LDL-C tended to be higher in the non-statin group than in the statin group, they were not significantly different (117.7 ± 28.5 mg/dL vs. 136.3 ± 25.3 mg/dL, P = 0.098).

### Discussion

The present study revealed that the average NYP and MYG in the statin group was lower than that in the non-statin group in pre-diabetic patients. These findings suggest the efficacy of statin therapy for plaque stabilization.

Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) have proposed a new guideline for the treatment of blood cholesterol to reduce the risk of ACVD, in which aggressive statin therapy is recommended for prevention.\(^{1)}\)

The effect of statin therapy on atherosclerotic plaque regression and stabilization has been reported by previous studies using intracoronary imaging modalities.\(^{10,23-25}\) On the other hand, in diabetic patients, the presence of plaque having a large necrotic core reduces the regressive change induced by statins.\(^{11-13)}\) Previous clinical studies showed that the absolute risk of myocardial infarction remains higher in patients with diabetes even
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**Table 2 Angioscopic Findings**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Statin (-)</th>
<th>Statin (+)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, n</td>
<td>7 (70%)</td>
<td>17 (94%)</td>
<td>0.116</td>
</tr>
<tr>
<td>LCx, n</td>
<td>7 (70%)</td>
<td>14 (78%)</td>
<td>0.674</td>
</tr>
<tr>
<td>RCA, n</td>
<td>8 (80%)</td>
<td>11 (61%)</td>
<td>0.417</td>
</tr>
<tr>
<td>Total number of yellow plaque</td>
<td>45</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Yellow grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (Light yellow)</td>
<td>14 (31%)</td>
<td>22 (47%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (Yellow)</td>
<td>22 (49%)</td>
<td>22 (47%)</td>
<td>0.094</td>
</tr>
<tr>
<td>Grade 3 (Intensive yellow)</td>
<td>9 (20%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Rupture, n</td>
<td>1 (10%)</td>
<td>2 (11%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Thrombus, n</td>
<td>6 (60%)</td>
<td>4 (22%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Multiple yellow plaques (≧2), n</td>
<td>9 (90%)</td>
<td>9 (50%)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Values are numbers (%).
LAD: left anterior descending artery, LCx: Left circumflex artery, RCA: right coronary artery.

Regarding glucose metabolic disorder, hyperglycemia accelerates the development of atherosclerosis through enhanced production of advanced glycation end products, oxidative stress, and vascular inflammation, which may contribute to diabetes-specific atherosclerosis, and diabetes modifies plaque morphology characteristics and thus interferes with plaque regression. Angioscopic indexes, both of the average NYP and MYG were higher in the statin group than in the non-statin group. Although there were differences in the above angioscopic indexes between the statin group and non-statin group, serum levels of LDL-C were not statistically different between the 2 groups. The present study results suggest that the effect of statin therapy, regarding glucose metabolic disorder, hyperglycemia accelerates the development of atherosclerosis through enhanced production of advanced glycation end products, oxidative stress, and vascular inflammation, which may contribute to diabetes-specific atherosclerosis, and diabetes modifies plaque morphology characteristics and thus interferes with plaque regression. Angioscopic indexes, both of the average NYP and MYG were higher in the statin group than in the non-statin group. Although there were differences in the above angioscopic indexes between the statin group and non-statin group, serum levels of LDL-C were not statistically different between the 2 groups. The present study results suggest that the effect of statins may be so-called pleiotropic effects on atherosclerotic lesions, which goes beyond lipid lowering. The pleiotropic effects include improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant effects, anti-inflammatory properties, and stabilization of atherosclerotic plaques.

The effect of plaque stabilization is mediated through not only reduction in lipids but also in macrophages. Because diabetes causes change in plaque macrophage characteristics, such pleiotropic effect by statins may be reduced in diabetic patients. Indeed, a study on intravascular ultrasound revealed that plaque regression induced by statins was less pronounced in patients with high HbA1c levels compared with that of patients with low HbA1c levels, although the decrease in LDL-C level was similar.
in both groups.\textsuperscript{13)}

The ACC and the AHA have revealed that in proportion to a 10-year ACVD risk, statin therapy is recommended to prevent cardiovascular events in patients without diabetes and history of cardiovascular disease.\textsuperscript{3} The 10-year ACVD risk was estimated from age, sex, race, the level of blood cholesterol, history of hypertension and diabetes, and smoking habit. From the viewpoint of preventive medicine, statins may be administered in the early stage of glucose metabolism disorder.

Conclusions

This angioscopic study showed evidence of plaque stabilization by statin therapy in pre-diabetic patients. Although recent guidelines showed that aggressive lipid-lowering statin therapy was recommended for the ACVD events in only diabetes patients, statin therapy may be required in the early stage of glucose metabolism disorder, such as pre-diabetes. Further clinical investigations will be necessary to create a basis for risk stratification and prevention of future cardiovascular events in patients with glucose metabolism disorder.

Limitations

The present study has several limitations. First, the findings are from a single center and are derived from a relatively small number of patients, and statistical significance was powerless in this small study. Especially, the serum LDL-C levels were not different between the statin and non-statin group. However, if more patients would have been included in this study, the statin effect may have been associated with the serum LDL-C levels.

Second, some patients were excluded because of the difficulty in acquiring angioscopic images. Therefore, some selection bias is inevitable. Third, the present study was limited by its retrospective nature, and the type, dosage, and duration of statin therapy were not unified. Prospective and large number of studies will guarantee the efficiency of statins for regression of coronary atherosclerosis in pre-diabetes patients.

Conflict of interest

W.S. received honorarium for lectures from Pfizer, Daiichi Sankyo Company, and Bristol-Myers Squibb, and donation for clinical researches from Daiichi Sankyo Company and Bristol-Myers Squibb. The other authors have no conflicts of interest.

References

14) Hiro T, Kimura T, Morimoto T, et al: Diabetes mellitus is a major negative determinant of coronary plaque regression during statin therapy in patients with acute coronary syndrome-serial intravascular ultrasound observations from the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary
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Syndrome Trial (the JAPAN-ACS Trial). Circ J 2010; 74:1165–1174