IT is well-known that the onset and progression of atherosclerosis is much more rapid in diabetic patients than healthy non-diabetic subjects, and one of the major causes of death in diabetes is atherosclerotic diseases. Thus, strict glycemic control is important to prevent the onset and progression of atherosclerosis. The UK Prospective Diabetes Study (UKPDS), a large-scale prospective study of newly diagnosed type 2 diabetic patients, showed that every 1% decrease of HbA1c could reduce the incidence of myocardial infarction and stroke by 14% and 11%, respectively [1]. However, the UKPDS failed to show a significant reduction in the incidence of stroke and myocardial infarction in the intensive glycemic control group (median HbA1c: 7.0%) compared with the conventional glycemic control group (median HbA1c: 7.9%) over 15 years [2]. These results suggest that much stricter glycemic control and an HbA1c below 7.0% may be needed to prevent atherosclerosis in diabetic patients. The Japan Diabetes Society (JDS) had proposed an HbA1c from 5.8% to 6.4% as a marker of good control, with less than 5.7% as excellent control. However, there is no evidence as to whether the risk of atherosclerosis can be decreased by further reducing HbA1c levels from the good control range (5.8–6.4%) to the excellent range (≤5.7%) in Japanese type 2 diabetic patients. Therefore, many diabetic patients with good control are maintained at such HbA1c levels, and no attempts are made to achieve excellent control.

We previously reported a method of measuring carotid artery intima-media thickness (IMT) by B-mode ultrasonography and showed that the IMT of subjects with diabetes was larger than that of age-matched subjects with normal glucose tolerance [3, 4]. Previous

Received: June 10, 2005
Accepted: October 26, 2005
Correspondence to: Dr. Yasushi TANAKA, Department of Medicine, Metabolism and Endocrinology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
large-scale prospective studies have shown that the baseline carotid IMT is significantly associated with the incidence of stroke or myocardial infarction during the observation periods of 7–10 years [5, 6]. Consequently, carotid IMT is currently thought to be a useful predictor of future atherosclerotic events and is used as a surrogate endpoint or intermediate point in clinical trials of therapy for atherosclerosis.

We preliminarily examined the change of IMT for retrospectively 3 years in 175 subjects with type 2 diabetes and a baseline HbA1c level between 5.8% and 6.4%. As shown in Fig. 1, age-adjusted annual increase rate of carotid artery IMT was positively correlated to 3-year mean HbA1c value (R = 0.32, p < 0.01). However, since this population included many subjects showing refrain of increase and decrease of HbA1c during 3 years, we could not conclude that carotid IMT increase was attenuated by keeping strictly-controlled HbA1c level. Therefore, we carefully extracted subjects without such fluctuation of HbA1c from this population, and examined the effect of strict glycemic control on IMT increase in the subjects with type 2 diabetes and a baseline HbA1c between 5.8% and 6.4% in a 3-year retrospective longitudinal study.

**Materials and Methods**

**Subjects**

As mentioned in introduction, a total of 175 subjects with type 2 diabetes who were aged 40–70 years at baseline (63 ± 1.3 years, mean ± SE) and had an HbA1c level between 5.8% and 6.4% (2000–2001) were primarily recruited from the outpatients of Juntendo University Hospital. Since the coefficient variance (CV) of the HbA1c assay system in our hospital was 0.9–1.0%, twice the standard deviation (SD) in 6.5% of HbA1c was ± 0.13%, we tentatively defined decrease or increase of HbA1c more than three times of SD (0.2%) as amelioration or deterioration of glycemic control. Among 175 subjects, 71 subjects showing refrain of increase and decrease more than 0.2% of HbA1c during 3 years from the baseline, and 4 subjects showed constant HbA1c within 0.2% of fluctuation were excluded. The remaining 100 subjects were classified into two groups: 67 subjects showing deterioration of the mean HbA1c during 3 years more than 0.2% from the baseline (D group) and 33 subjects showing improvement of the mean HbA1c more than 0.2% from baseline (A group); these groups were analyzed in the study. Every subject visited to our hospital ever 1 or 2 months, and received general check and blood examination. The diagnosis of type 2 diabetes was based on the current WHO criteria [7]. The clinical characteristics and the annual increase rate of carotid artery IMT during the observation period were compared between the two groups in a 3-year retrospective longitudinal study.

**Assessment of carotid IMT**

Ultrasoundographic scanning of the carotid arteries was performed using an echotomography system (EUB-555; Hitachi Medico, Tokyo) with a linear transducer (mid-frequency range of 7.5–10 MHz). Scanning of the extracranial carotid arteries in the neck was performed bilaterally in three different longitudinal projections (i.e. anterior-oblique, posterior-oblique, and lateral). This allowed the common carotid artery, carotid bulb, and internal and external carotid arteries to be scanned, with all of these structures being measured as completely as possible. It was difficult to measure all these structures in some patients, but the common carotid artery could always be detected, and so we limited evaluation of IMT to the common carotid artery in this study.

The IMT was defined as previously reported [3, 4, 8]. Briefly, it represented the distance from the leading edge of the first echogenic line to the leading edge of
the second echogenic line on the scans, with the first line corresponding to the lumen-intimal interface and the second line corresponding to the collagen-containing upper layer of the adventitia. Plaque was defined as a localized area with a thickness ≥1.4 mm. In each longitudinal projection, the site of the greatest IMT thickness (including plaque) was detected by scanning along the common carotid artery. Three measurement of the IMT were made, i.e. at the site of greatest thickness and at two other points (1 cm proximal and 1 cm distal to this site), and the highest value of the 6 averaged IMT (3 from the left side and 3 from the right side) were used as the representative IMT value for each patients. The scanning period averaged 30 min and scanning was always performed by a physician. The reproducibility of the IMT measurement was described in our previous report demonstrating good reproducibility [3, 4].

Each patient received carotid IMT measurement every one year or one and half years, and 315 IMT measurements were done during the study period (average 3.15 measurements of IMT for each subject). A linear regression line was drawn for sequential determination of IMT as a dependent variable, and the annual increase rate of IMT was calculated as the slope of this regression line for each patient. Annual increase rate of IMT was adjusted for age and other clinical factors (age, BMI, HbA1c, SBP, DBP, and serum lipids) by analysis of covariance (ANOCOVA).

Statistical analysis

Data are presented as the mean±SE. Laboratory values and clinical factors of each group were compared by the paired t-test. Student’s t-test was used to compare mean values between the two groups, whereas the χ²-test was used to compare percentages.

Results

The characteristics of the subjects at baseline (2000–2001) are shown in Table 1. None of the parameters was significantly different between the two groups. The average values of the clinical parameters during the observation period and carotid artery IMT at baseline and at the end of observation period are displayed in Table 2. The mean HbA1c of the A group was significantly lower than that of the D group. Other factors were not significantly different between the two groups, and no significant changes from the baseline were observed in either group. The mean baseline IMT did not differ between the two groups, but the mean IMT at the end of the study was significantly smaller in A group than in D group.

Comparison of the drug therapy between the two groups is shown in Table 3. All patients with insulin injection used regular insulin or rapid insulin analogue three times a day with or without NPH insulin or long acting insulin analogue before bedtime. While the percentage of patients using insulin, the daily insulin dosage and injection times did not differ between the two groups (15%, 16 ± 2.2 U, 3.2 ± 0.8 times, mean ± SE, in A group vs. 9.0%, 14 ± 2.1 U, 3.3 ± 0.5 times, in D group), the use of oral anti-diabetic agents was signifi-
Table 3. Comparison of the drug therapy between the two groups

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>D group</th>
<th>A group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin</td>
<td>6 (9)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>oral agents</td>
<td>55 (82)</td>
<td>13 (39)</td>
</tr>
<tr>
<td>SU/Nateglinide</td>
<td>16/13</td>
<td>2/2</td>
</tr>
<tr>
<td>Metformin/Pioglitazone</td>
<td>10/1</td>
<td>3/1</td>
</tr>
<tr>
<td>α-Gl</td>
<td>15 (22)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Antihyperlipidemic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>statin</td>
<td>14 (21)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>fibrate</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>15 (22)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>3/14</td>
<td>0/3</td>
</tr>
<tr>
<td>β-b/β-b</td>
<td>2/1</td>
<td>1/0</td>
</tr>
<tr>
<td>Antithrombotic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aspirin</td>
<td>9 (13)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>cilostazol / ticlopidine</td>
<td>8/3</td>
<td>3/4</td>
</tr>
</tbody>
</table>

SU: sulfonylurea, α-Gl: α-glucosidase inhibitor, CCB: calcium channel blocker, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, β-b: β-blocker, α-b: α-blocker, *p<0.01 vs. D group

significantly lower in A group than in D group (39% vs. 82%, $\chi^2 = 16.6$, $p<0.001$). The use of lipid-lowering agents did not differ between the two groups (22% vs. 21%), but anti-hypertensive agents were used by significantly less of A group than D group (27% vs. 52%, $\chi^2 = 4.83$, $p = 0.032$).

The annual mean HbA1c values of the study subjects are shown in Fig. 2. While the annual mean HbA1c values did not differ between the two groups during the first year (5.90 ± 0.10 in A group vs. 6.02 ± 0.09 in D group), the annual mean values of the second and the third year were significantly lower in A group than in D group (5.60 ± 0.11 vs. 6.33 ± 0.09 in the second year, $p<0.001$; 5.62 ± 0.12 vs. 6.50 ± 0.11 in the third year, $p<0.001$). Regarding other clinical factors, the annual mean values of BMI, systolic blood pressure, diastolic blood pressure, and serum lipids were not significantly different between the two groups.

Fig. 1 showed a positive correlation between the age-adjusted annual increase rate of IMT and the 3-year mean HbA1c values in the primarily recruited 175 subjects. As shown in Fig. 3, the adjusted annual increase rate of IMT was significantly smaller in A group than in D group ($-0.035 \pm 0.019$ vs. $0.036 \pm 0.015$ mm, mean ± SE, $p<0.001$).

Discussion

From the background data for primarily recruited 175 subjects shown in Fig. 1, we speculated that strict glycemic control may prevent IMT increase in type 2 diabetic subjects. The present study demonstrated that deterioration of glycemic control from a good HbA1c values between 5.8% and 6.4% promoted an increase of IMT in type 2 diabetic patients, while further improvement of glycemic control prevented an increase of IMT. The annual increase rate of IMT adjusted for other clinical factors was significantly smaller in A group than in D group, and it was actually a negative value in A group, meaning that regression of IMT from the baseline was achieved by near normalization of
HbA1c level for three years.

Pioglitazone, metformin and α-glucosidase inhibitor, voglibose, were previously reported to reduce the IMT increase independently of glycemic control in type 2 diabetic patients [11–13]. While these oral agents having extra-pancreatic actions did not differ between the two groups, the proportion of the patients with insulin secretagogue (sulfonylurea or nateglinide) was significantly lower in A group than in D group (12% vs. 43%, χ² = 9.71, p = 0.002) as shown in Table 3. However, A group showed a quite good glycemic control as mean HbA1c 5.67%, suggesting a higher proportion of patients with improved compliance for diet and exercise therapies during the observation period, and a lower proportion of patients with disturbed intrinsic insulin secretion in A group than in D group.

We previously evaluated the IMT by a cross-sectional study in healthy non-diabetic subjects and type 2 diabetic patients, and found that the IMT showed an age-dependent increase in both groups, while the IMT of the diabetic group was much greater than that of the age-matched healthy group [3, 4]. Thereafter, we prospectively followed IMT in type 2 diabetic patients for 4 years, and observed that the annual increment was about 0.04 mm/year (unpublished data), and remarkably higher than that reported previously in healthy subjects (0.007–0.008 mm/year) [9, 10], suggesting that diabetic state is a potent promoter of atherosclerosis. While the annual increase rate of IMT in D group was consistent with such data, the present study showed significant IMT regression in A group (a negative annual change). As shown in Table 2, the baseline IMT of both groups was already much higher compared with that reported previously in age-matched non-diabetic healthy subjects. The present results for A group suggest that the excessive IMT of diabetic patients can be improved by strict glycemic control alone, since other clinical data (such as BP, serum lipids, and BMI) were not different between the two groups as can be seen in Table 2. However, the present investigation was a 3-year retrospective longitudinal study with a small number of patients, and the use of oral anti-diabetic agents and anti-hypertensive agents was significantly different between the two groups. Thus, we should further investigate the significance of long-term improvement in HbA1c for IMT progression and incidence of atherosclerosis-related events. We have started a prospective study on the effect of strict glycemic control with a uniform drug therapy protocol in type 2 diabetic patients, and this study may eventually confirm the present findings and may give us a clue to settle the target level of HbA1c.

The DECODE study was a meta-analysis of 13 large-scale prospective studies performed in Europe [14], and it showed a higher mortality rate due to atherosclerosis in subjects with mild type 2 diabetes or impaired glucose tolerance (IGT), who had normal fasting plasma glucose levels but higher glucose levels at 2-h after an oral glucose load, than in subjects with normal glucose tolerance (NGT). Similarly, the Hisayama study, a long-term prospective cohort study performed by Kyushu University in Japan, showed a higher incidence of stroke and coronary artery disease in subjects with type 2 diabetes and IGT compared with that in subjects with NGT [15]. Interestingly, Hanefeld et al. reported that acarbose, an α-glucosidase inhibitor, improved postprandial hyperglycemia and attenuated IMT increase in IGT subjects [16]. These studies suggest that strict glycemic control may prevent the development or progression of atherosclerosis, not only in mild type 2 diabetic patients but also in persons with IGT. Taken together, these results suggest that the target for glycemic control may ultimately be normalization of plasma glucose for complete prevention of hyperglycemia-induced progression of atherosclerosis. Accordingly, a large-scale prospective study of subjects with IGT and mild type 2 diabetes is needed for clarification of this point.

In addition to hyperglycemia, hyperlipidemia, and hypertension, another significant risk factor for atherosclerosis in diabetics is a thrombotic tendency. The American Diabetes Association (ADA) recommends low-dose aspirin therapy for both primary and secondary prevention of atherosclerotic events [17]. However, a recent large-scale prospective study, The Primary Prevention Project (PPP) Trial, failed to demonstrate significant primary prevention of cardiovascular events in diabetics by low-dose aspirin use [18]. This report suggests that aspirin-insensitive mechanisms of platelet activation and thrombus formation may exist in diabetics. Cilostazol is a different type of antiplatelet agent that inhibits type 3 phosphodiesterase in platelets and decreases thromboxane formation by enhancement of the platelet cAMP level. We prospectively evaluated the effect of cilostazol on carotid IMT in Japanese type 2 diabetic patients for a mean period of 2.6 years, and observed attenuating effect of IMT increase [19]. Since this was a small short-term trial and the results
were limited, we have started an international prospective trial, involving Japan, Korea, China, and the Philippines, to evaluate the anti-atherogenic effect of cilostazol compared with low-dose aspirin in type 2 diabetic patients using carotid IMT as a surrogate endpoint as well as the incidence of cardiovascular events for 5 years.

In conclusion, further improvement of glycemic control from a good HbA1c value prevented an increase of IMT in type 2 diabetic patients. A large-scale prospective study is needed to confirm the present findings.

References