Seven-year Observational Study on the Association between Glycemic Control and the New Onset of Macroangiopathy in Japanese Subjects with Type 2 Diabetes

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Abstract

Objective To examine the association between glycemic control and the new onset of macroangiopathy in Japanese subjects with type 2 diabetes.

Methods We examined seven-year follow-up data for 572 patients. We divided the subjects by the average of seven-year glycemic control based on the guidelines. First, we excluded the subjects with a past history of macroangiopathy and then examined the incidence of the new onset of macroangiopathy.

Results The incidence of ischemic heart disease (IHD) was 1.0% per year, and that of cerebral vascular disease (CVD) was 1.0% per year. However, IHD events were not observed at all for five years in the most intensive glycemic control group (HbA₁c<6%). Similarly, CVD events were not observed at all for seven years in the most intensive glycemic control group (HbA₁c<6%). In addition, the cumulative incidence rate of IHD tended to increase as the glycemic control became poorer (HbA₁c<6%, 4.5%; 6≤HbA₁c<7%, 6.0%; 7≤HbA₁c<8%, 7.2%; HbA₁c≥8%, 10.7%). Furthermore, a logistic regression analysis showed that the duration of diabetes and HbA₁c level were independent risk factors contributing to the onset of IHD, but not to the onset of CVD.

Conclusion This seven-year observational study showed the possible association between glycemic control and the onset of macroangiopathy in a total of 572 Japanese subjects with type 2 diabetes.

Key words: meticulous glycemic control, ischemic heart disease, cerebral vascular disease


Introduction

Several large clinical trials including the Diabetes Control and Complications Trial (DCCT), United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto studies have demonstrated that strict glycemic control prevents the onset of microangiopathy in subjects with type 1 and type 2 diabetes (1-3). In contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) studies failed to show the effect of strict glycemic control on the onset of macroangiopathy (4, 5). Furthermore, the ACCORD study showed that strict glycemic control leads to an increased number of deaths, which was concluded to have been due to severe hypoglycemia induced by intensive glycemic control. Then, longer-duration studies (over 15 years) including Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) and
UKPDS80 demonstrated the significance of strict glycemic control from the early stage of diabetes on the onset of macroangiopathy (6, 7). In Japan, however, there is little evidence about the significance of strict glycemic control on the onset of macroangiopathy. In Japan, it is recommended to maintain “HbA1c<7.0%” (NGSP) (8) in order to prevent the onset and/or progression of diabetic complications. In this study, we examined the association between glycemic control and the onset of macroangiopathy in Japanese subjects with type 2 diabetes.

Materials and Methods

Study population and patient preparation

Subjects who visited the outpatient clinic of diabetes at Kawasaki Medical School Hospital from 2000 to 2002 and whose time course we could follow for more than seven years were eligible for this study. In addition, the subjects were those who fulfilled the following criteria: (1) without severe liver dysfunction, (2) without infectious disease, malignancy or various endocrine diseases and (3) not using steroid drug. The hospital ethics committee approved the study protocol, and we provided public information on the study via the Internet, instead of obtaining informed consent from each patient. We performed data collection for variables such as type of medication and smoking status, as well as biochemical data, intensively for three months from August to October every year, in order to reduce the effect of seasonal variation in various variables such as blood pressure and HbA1c level.

We divided the subjects by the average HbA1c value for seven years into four groups based on the guidelines of the Japan Diabetes Society as follows: group 1, HbA1c<6%; group 2, 6%≤HbA1c<7%; group 3, 7%≤HbA1c<8%; and group 4, HbA1c≥8%. We compared the frequency of onset of macroangiopathy for seven years among these four groups. The diagnosis of the occurrence of ischemic heart disease (IHD) events was performed by cardiologists based on the clinical symptoms (chest pain), characteristic electrocardiography (ECG) changes (ST change), cardiac enzyme levels (elevated cardiac enzymes) and the findings in coronary angiography (stenosis) and/or echocardiography (ventricular asynergy), according to established guidelines. Cerebral vascular disease (CVD) was defined as a validated definite or probable hospitalized cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage diagnosed by neurosurgical experts based on the clinical symptoms and neuroimaging findings, according to the established guidelines. In addition, we used the duration of diabetes, BMI, metabolic parameters and blood pressure as possible risk factors contributing to the onset of macroangiopathy.

Hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg or current use of antihypertensive agents. Dyslipidemia was defined as low density lipoprotein (HDL) cholesterol <40 mg/dL, triglycerides ≥150 mg/dL or current use of lipid-lowering agents. Each target value was set by the Japan Diabetes Society. Diabetic neuropathy was defined as having a subjective and/or objective symptom. The presence of diabetic retinopathy was defined as having simple diabetic retinopathy or more severe retinopathy that had been diagnosed by ophthalmologists based on the findings of fundoscopy. The presence of diabetic nephropathy was defined as having albuminuria (urinary albumin excretion ≥30 mg/g creatinine). Best possible treatment was performed for diabetes, hypertension and dyslipidemia. In addition, it should be noted that we were very careful to avoid hypoglycemia while treating patients.

Statistical analysis

The statistical analyses were performed using StatView statistical software (Version 5.0) on a personal computer. A multiple comparison analysis was performed using the Tukey-Kramer method. χ² test was used for the comparison of micro- and macroangiopathy at the entry point and the comparison of various parameters between the presence and absence of the new onset of macroangiopathy. Kaplan-Meier test was used for evaluation of the cumulative incidence rates of IHD and CVD. Log-rank test was used to compare the frequency of new onset of macroangiopathy. The logistic regression method was used to analyze the factors contributing to the onset of ischemic heart disease and cerebral vascular disease.

Results

A total of 572 subjects were enrolled in this study. The characteristics of the study subjects at baseline were as follows: age, 62.8±9.9 years old; BMI, 23.9±3.6 kg/m²; duration of diabetes, 12.0±8.7 years; and HbA1c 7.1±1.1% (NGSP). As shown in Table 1, the numbers in the different HbA1c categories were as follows: HbA1c<6%, n=22; 6%≤HbA1c<7%, n=200; 7%≤HbA1c<8%, n=260; and HbA1c≥8%, n=90. There was no difference among these four groups in systolic and diastolic blood pressure (Table 1). In addition, there was no difference among these four groups in LDL and HDL cholesterol and triglyceride levels, except for higher LDL cholesterol levels in group 4. There was also no difference among these four groups in smoking status (Table 1). Age in group 4 at the entry point was younger than in the other groups, and BMI and duration of diabetes in group 4 were greater than those in the other groups.

Table 2 shows the average clinical data for seven years. Average HbA1c levels for seven years in these four groups were 5.8±0.2%, 6.6±0.3%, 7.5±0.3% and 8.7±0.7%, respectively. There was no difference during the observation period in the average systolic and diastolic blood pressure among the groups (Table 2), just as observed at the entry time point. In addition, there was no difference among the four groups in LDL and HDL cholesterol and triglyceride levels, except for higher LDL cholesterol and triglyceride.
levels in group 4 (Table 2). Average BMI in group 4 was higher than in the other groups. Moreover, each lipid parameter had attained a value within the range aimed for by the management in all of the groups. There was no difference among the four groups in the frequency of use of anti-hypertensive drugs, statins and pioglitazone at the entry point. Insulin and α-glucosidase inhibitor usage rates were higher in the group with a higher HbA1c level, and the sulfonylurea (SU) usage rate was the highest in the 7% < HbA1c < 8% group (Table 3). In addition, we examined the correlations between the average HbA1c level and other values. In terms of the results, the BMI and duration of diabetes had weak but significant positive correlations with the average HbA1c level (BMI, r = 0.215, p < 0.0001; duration, r = 0.205, p < 0.0001).

The frequencies of IHD at the start of the observation period in the four groups were as follows: group 1, 0%; group 2, 8.5%; group 3, 9.2%; and group 4, 16.7%. A higher frequency of IHD was observed in subjects with poorer glycemic control. The frequency in group 4 was significantly higher than that in group 1 or group 2. The frequencies of CVD at the start of the observation period in the four groups were as follows: group 1, 4.5%; group 2, 6.0%; group 3, 6.5%; and group 4, 3.3%. There was no significant difference among these four groups (Table 4). The frequency of neuropathy at the start of the observation period was as follows: group 1, 13.6%; group 2, 33.0%; group 3, 51.9%; and group 4, 71.1%. The frequency of retinopathy at the start of the observation period was as follows: group 1, 13.6%; group 2, 24.0%; group 3, 31.5%; and group 4, 52.2%. The frequency of nephropathy at the start of the observation period was as follows: group 1, 13.6%; group 2, 33.0%; group 3, 51.9%; and group 4, 71.1%. The frequency of microangiopathy at the start of the observation period was as follows: group 1, 9.1%; group 2, 17.5%; group 3, 24.6%; and group 4, 32.2%. A higher frequency of microangiopathy was observed in subjects with poorer glycemic control (Table 4).

First, we excluded the subjects with a past history of diabetes, hypertension, and dyslipidemia (Table 3).
Table 4. Frequency of Diabetic Complications at the Baseline.

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>IHD (%)</th>
<th>CVD (%)</th>
<th>Neuropathy (%)</th>
<th>Retinopathy (%)</th>
<th>Nephropathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6%</td>
<td>0 (0%)</td>
<td>1 (4.5%)</td>
<td>3 (13.6%)</td>
<td>3 (13.6%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>6%&lt;HbA1c&lt;7%</td>
<td>17 (8.5%)</td>
<td>12 (6.0%)</td>
<td>66 (33.0%)</td>
<td>48 (24.0%)</td>
<td>35 (17.5%)</td>
</tr>
<tr>
<td>7%&lt;HbA1c&lt;8%</td>
<td>24 (9.2%)</td>
<td>17 (6.5%)</td>
<td>135 (51.9%)</td>
<td>82 (31.5%)</td>
<td>64 (24.6%)</td>
</tr>
<tr>
<td>HbA1c≥8%</td>
<td>15 (16.7%)</td>
<td>3 (3.3%)</td>
<td>64 (21.1%)</td>
<td>47 (17.2%)</td>
<td>29 (32.2%)</td>
</tr>
</tbody>
</table>

* p<0.05 vs. HbA1c<6%, § p<0.05 vs. 6%<HbA1c<7%, † p<0.05 vs. 7%<HbA1c<8%.

Figure. A Kaplan-Meier analysis of the onset of IHD in subjects with various HbA1c levels.

Table 5. Logistic Regression Analysis to Determine the Independent Factors Contributing to the Onset of IHD (a) and CVD (b). Numbers in Parentheses Indicate the Values after Adjustment with Age and Sex.

(a) | Odd ratio | 95%CI | p value |
---|-----------|-------|---------|
Duration (year) | 1.073 (1.058) | 1.038-1.108 (1.022-1.104) | <0.0001 (0.001) |
BMI (kg/m^2) | 1.028 (1.041) | 0.936-1.130 (0.943-1.149) | 0.564 (0.425) |
HbA1c (%) | 1.458 (1.676) | 1.034-2.056 (1.153-2.463) | 0.031 (0.007) |
Systolic BP (mmHg) | 0.986 (0.981) | 0.955-1.017 (0.950-1.013) | 0.371 (0.240) |
Triglyceride (mg/dL) | 1.004 (1.004) | 0.998-1.010 (0.998-1.010) | 0.239 (0.184) |
LDL chol (mg/dL) | 0.986 (0.989) | 0.970-1.003 (0.973-1.006) | 0.098 (0.208) |

(b) | Odd ratio | 95%CI | p value |
---|-----------|-------|---------|
Duration (year) | 1.016 (1.003) | 0.972-1.063 (0.958-1.051) | 0.481 (0.888) |
BMI (kg/m^2) | 1.029 (1.043) | 0.921-1.150 (0.927-1.174) | 0.609 (0.484) |
HbA1c (%) | 0.895 (1.031) | 0.543-1.477 (0.604-1.758) | 0.664 (0.911) |
Systolic BP (mmHg) | 1.010 (1.010) | 0.970-1.051 (0.969-1.052) | 0.637 (0.637) |
Triglyceride (mg/dL) | 1.003 (1.004) | 0.996-1.010 (0.996-1.011) | 0.409 (0.360) |
LDL chol (mg/dL) | 0.989 (0.993) | 0.969-1.009 (0.973-1.014) | 0.272 (0.513) |

Macroangiopathy and then examined the incidence of the new onset of macroangiopathy in the seven-year follow-up period. In terms of the results, the incidence of the new onset of IHD in subject without a past history macroangiopathy was 1% per year during the seven-year follow-up period. In addition, the cumulative incidence rate of IHD tended to be increased as the glycemic control became poorer (HbA1c<6%, 4.5%; 6%<HbA1c<7%, 6.0%; 7%< HbA1c<8%, 7.2%; HbA1c>8%, 10.7%), but this did not reach statistical significance (Figure). A logistic regression analysis showed that the duration of diabetes and HbA1c level were independent risk factors contributing to the new onset of IHD, but LDL cholesterol, triglyceride, systolic blood pressure and BMI were not independent risk factors (Table 5a). Similar results were observed even after adjustment for age and sex (Table 5a). In addition, we compared various parameters between the subjects with and without IHD. Age was significantly higher in subjects with ischemic heart disease than in those without it (p<0.006), but there was no difference for the other factors (HbA1c, BMI, dura-
tion, triglyceride, HDL cholesterol, LDL cholesterol and blood pressure). Furthermore, we compared insulin and SU usage and the presence of microangiopathy between the subjects with and without IHD. Insulin usage rate and the presence of diabetic retinopathy were higher in the new onset of IHD group than in the non-onset group. Therefore, we compared various parameters including insulin usage and the presence of diabetic retinopathy by logistic analysis. However, similar results were obtained and these parameters were found not to be independent factors [insulin usage, p=0.954 (p=0.803, upon adjustment for age and sex); presence of diabetic retinopathy, p=0.440 (p=0.420, upon adjustment for age and sex)]. The incidence of new onset of CVD in subjects without a past history of macroangiopathy was 1% per year during the seven-year follow-up period. There was no difference in the cumulative incidence rate of CVD (HbA1c<6%, 9%; 6%<HbA1c<7%, 6.5%; 7%<HbA1c<8%, 3.4%; HbA1c>8%, 3.4%). It is notable, however, that CVD events were not observed at all for seven years in the most intensive glycemic control group (HbA1c<6%). Logistic regression analysis showed that no factors, including duration of diabetes, HbA1c level, LDL cholesterol level, triglyceride, systolic blood pressure and BMI, were independent risk factors contributing to the onset of CVD (Table 5b). Similar results were observed even after adjustment for age and sex (Table 5b). In addition, we compared various parameters between the subjects with and without CVD. Similarly, age was significantly higher in the onset group than in the non-onset group (p<0.014), but there was no difference for the other factors (HbA1c, BMI, duration, triglyceride, HDL cholesterol, LDL cholesterol and blood pressure). We compared insulin and SU usage and the presence of microangiopathy between the subjects with and without CVD in the same way as for IHD. Diabetic retinopathy was more common in the new onset of IHD group than in the non-onset group. However, similar results were obtained, and diabetic retinopathy was not an independent factor associated with the new onset of CVD [p=0.852 (p=0.738, after adjusting for age and sex)].

Discussion

Recently, the number of diabetic patients has increased markedly all over the world, especially in Asia. From a national nutrition survey that was performed in Japan in 2012, the total number of subjects with diabetes mellitus or impaired glucose tolerance was estimated to be over 20 million. The final goals for diabetic subjects are to secure years of healthy life and to maintain the quality of life, just as in healthy subjects. In order to achieve these goals, it is very important to prevent the onset and progression of diabetic macroangiopathy. A recent large clinical trial that was performed outside of Japan showed that strict control from an early stage concerning blood glucose levels and several other risk factors is crucial for the prevention of macroangiopathy (9). In Japan, the Hisayama study showed that the numbers of IHD events per 1,000 person/years were 3.5 in males and 1.8 in females, and those of CVD events were 5.3 in males and 3.9 in females in the general population, including patients with diabetes and impaired glucose tolerance (IGT) at a rate of about 30% (10). When these were limited to diabetic patients, such numbers of IHD and CVD events were 5.0 and 6.5, respectively. In the interim report of Japan Diaberes Complications Study (JDCS) (11), the numbers of IHD and CVD events per 1,000 person/years were 9.6 and 7.6, respectively, both of which were higher than those in the Hisayama study reported about 10 years ago.

In this study, the annual incidence rates of both IHD and CVD were 1.0%, being slightly higher than those in JDCS. The data in the Steno 2 study suggest that the onset of macroangiopathy is influenced by the control of dyslipidemia and hypertension, as well as diabetes. In this study, there was no difference in the blood pressure level for seven years among the four groups. There was also no difference in the LDL and HDL cholesterol levels between group 1 and the other groups, although there was a significant difference in triglyceride levels between group 1 and group 4. Furthermore, all levels (LDL and HDL cholesterol and triglyceride) in the four groups were within the ranges aimed for by management for seven years. Thus, we think that the possibility that hypertension and/or dyslipidemia influenced the difference of the onset of macroangiopathy between group 1 and the other groups could be ruled out. Smoking is also one of the well-known risk factors for increasing the onset of IHD (12), but there was no difference among the four groups in smoking. In addition, there was no difference among the four groups in the frequency of use of antihypertensive agents, statins and pioglitazone at the entry point. Generally, the inappropriate use of insulin and SU increases cardiovascular disease through the induction of hypoglycemia. However, there was no severe hypoglycemia in this study, since each doctor paid sufficient attention to the presence of hypoglycemia. It has been reported that α-glucosidase inhibitor and biguanide drugs exert a suppressive effect on macroangiopathy, but these drugs tended to be used more frequently in the poor control group in this study. Therefore, we think that we could rule out the possibility that these drugs influenced the difference of the onset of macroangiopathy. It should be noted here that we were very careful to avoid hypoglycemia while treating patients. Needless to say, the avoidance of hypoglycemia is very important when we perform strict glycemic control in order to decrease the incidence of macroangiopathy. In fact, we examined the hypoglycemic episodes in the medical records of patients who developed new-onset macroangiopathy during the follow-up period, but failed to find any episodes of severe hypoglycemia.

This study is associated with some limitations. In the group with the poorest glycemic control, the duration of diabetes was longer than in the other groups, and BMI was highest among the four groups. Moreover, there were more
subjects being treated with insulin than in the other groups. Generally, the incidence of macroangiopathy is higher in obese subjects than in non-obese ones. We cannot say that the artery condition of patients with long diabetic duration is “good”. This study is retrospective and we cannot rule out the possibility that the difference of these background factors affected the result. However, since this is a long-term observation study with a substantial number of subjects, the findings are considered to indicate the importance of glucose control in daily clinical practice. Taken together, this seven-year observational study showed the possible association between glycemic control and the onset of macroangiopathy in a total of 572 Japanese subjects with type 2 diabetes.

All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.


References


