【 ORIGINAL ARTICLE 】

Influence of Timing of Insulin Initiation on Long-term Glycemic Control in Japanese Patients with Type 2 Diabetes: A Retrospective Cohort Study

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Abstract:
Objective   Delays in insulin initiation can lead to the development of complications in the management of type 2 diabetes.
Methods   In this study, the effects of the timing of insulin initiation on glycemic control in patients with type 2 diabetes were evaluated retrospectively. Changes in the HbA1c levels of 237 patients were analyzed after insulin initiation.
Results   The patients were divided into 4 groups according to the duration of diabetes at the time of insulin initiation: ≤3 years, 4 to 6 years, 7 to 9 years, or ≥10 years. Patients with a diabetes duration of ≤3 years were more frequently hospitalized at the time of insulin initiation, had a higher HbA1c level before insulin initiation and a lower HbA1c level at 1 year after insulin initiation and exhibited significant decreases in HbA1c at 1, 3, or 5 years after insulin initiation than those in the other 3 groups with longer durations of diabetes. In the group receiving 4 insulin injections per day, the reduction in HbA1c after 5 years of treatment was larger in patients with a diabetes duration at the time of insulin initiation of ≤3 years than in those with a duration of 7 to 9 years or ≥10 years.
Conclusion   Our results suggested that an earlier initiation of insulin therapy was crucial for sustaining glycemic control in Japanese patients with type 2 diabetes, particularly in those with a history of obesity or receiving multiple insulin injections daily.

Key words: type 2 diabetes, insulin initiation, glycemic control

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Introduction

Earlier glucose control can reduce the risk of both macrovascular and microvascular complications in patients with diabetes (1). Insulin therapy provides a potent anti-hyperglycemic effect in most types of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a legacy effect in which the beneficial effects of pre-vious early interventions consisting of glycemic control with insulin, sulfonylurea, or metformin on both micro- and macro-vascular risks and lifespan were able to be sustained for a decade despite a loss of between-group differences in glucose control after the first year of intervention (2).

Sequential treatment algorithms with antidiabetic agents have been proposed in the guidelines established by the American Diabetes Association and the European Association for the Study of Diabetes for the treatment of type 2

diabetes (3). The first-line treatment consists of an oral antidiabetic drug, such as metformin, for most cases of type 2 diabetes, except for those with marked hyperglycemia (high HbA1c), an insulin-dependent state, diabetic ketoacidosis, or hyperosmolar hyperglycemic syndrome. However, an oral pharmacological approach remains difficult in a significant number of cases with type 2 diabetes in terms of sustainable glycemic control, despite combinations of multiple different classes of agents. Insulin therapy is needed to improve hyperglycemia in patients in whom treatment with multiple agents has failed.

Insulin resistance and pancreatic β-cell dysfunction are 2 major components in the pathogenesis of type 2 diabetes (4). Among subjects with a normal glucose tolerance, Asian subjects had a higher insulin sensitivity and a lower insulin secretion than Caucasian and African subjects (5). Asian or Japanese non-obese patients with type 2 diabetes are characterized by a reduction in insulin secretion caused by a reduced β-cell function, even though insulin resistance is generally milder than that seen in Caucasian patients with diabetes (6-8). Hence, the preservation of the β-cell function by reducing the β-cell overload with the supplementation of insulin at an early stage of diabetes seems to be important for the long-term management of diabetes in Japanese patients. However, evidence demonstrating the impact of the timing of insulin initiation on glycemic control is limited.

In the current retrospective study, we aimed to examine the effects of the timing of insulin initiation in patients with type 2 diabetes on glycemic control in terms of the disease duration, age, and the injection frequency of insulin.

Materials and Methods

The study protocol was approved by the Medical Ethics Committee of the Yokohama City University Hospital, and the study was performed in accordance with the Declaration of Helsinki. The patients were anonymized to protect their personal information. All methods were performed in accordance with the relevant guidelines and regulations. As a retrospective study, the opt-out method of obtaining informed consent was adopted.

This retrospective study was conducted using the in- and out-patient medical records of patients attending Yokohama City University Hospital, Yokohama, Japan; Chigasaki Municipal Hospital, Chigasaki, Japan; and Nakajima Naika Clinic, Yokosuka, Japan. Patients whose records contained data for at least 5 years after the initiation of insulin injection, who were ≥20 years old, who had been diagnosed with type 2 diabetes, who were receiving insulin injections, and whose HbA1c levels had been measured at the start of insulin injection and at 3 and 5 years after insulin initiation were included in the study.

Based on the study criteria, 237 patients who met the study criteria were included in the study. The age at the time of the diagnosis of diabetes and at insulin initiation, sex, history of obesity, and HbA1c level before and at 1, 3,

and 5 years after the start of insulin initiation were retrieved from the medical records. The duration of diabetes was determined by 1) a letter of reference from other clinics or hospitals, 2) doctor's questions, or 3) the patient's medical interview sheets. The patients were divided into 4 groups according to the duration of diabetes, as follows: ≤3 years, 4 to 6 years, 7 to 9 years, and ≥10 years. The patients were also divided according to their age or the frequency of daily insulin injections. The changes in the HbA1c levels at 1, 3, and 5 years, relative to the baseline values, were then evaluated. The "history of obesity" was defined as the presence of a body mass index (BMI) >25 at baseline, during the follow-up period, or at any point previously according to their medical record. The frequency of insulin injections per day was determined according to the frequency of daily insulin injection at the baseline after excluding subjects who changed the frequency during the follow-up period.

Differences between two groups were analyzed by Student's t-test. For comparisons among more than two groups, a one-way analysis of variance was used to determine the presence of differences among groups, and a multiple comparison procedure (Tukey's tests) was used to isolate the differences. The statistical calculations were performed using the SPSS software program, ver. 20 (IBM Japan, Tokyo, Japan). Differences were considered significant at $p<0.05$. The mean±standard deviation was used to summarize continuous variables and frequency, and the percentage was used to summarize the categorical variables.

Results

Of the 237 patients included in this study, the mean age at the time of the diagnosis of diabetes was 50.39±11.28 years, the mean age at the time of insulin initiation was 60.49±10.80 years, and 131 (55.2%) subjects were men (Table 1). Overall, 21.7% of the patients had a history of obesity, and insulin injection was initiated during hospitalization in 58.5%. The mean HbA1c level before the initiation of insulin was 10.35±2.01%, and the mean HbA1c levels at 1, 3, and 5 years after insulin initiation were 7.55±1.27% (-2.90± 2.93% from baseline, n=230), 7.45±1.27% (-2.80±2.84% from baseline, n=239), and 7.50±1.36% (-3.06±3.24% from baseline, n=238), respectively.

The patients were divided into 4 groups based on the duration of diabetes: ≤3 years (n=65), 4 to 6 years (n=25), 7 to 9 years (n=32), and ≥10 years (n=115) (Table 1). Patients with a diabetes duration of ≥10 years had a significantly lower age at the time of the diabetes diagnosis (46.90±9.50 years, p<0.01) and a significantly higher age at the time of insulin initiation (63.51±8.89 years, p<0.01) than the other groups. In contrast, patients with a diabetes duration of ≤3 years had been hospitalized at the time of insulin initiation more frequently than in the other groups (63.60%, p<0.01). These patients also had a higher HbA1c level before insulin initiation (11.52±2.34%, p<0.01) and a lower HbA1c level at 1 year after the start of insulin injection (7.10±1.49%, p<

Table 1.   Characteristics of Patients.

Duration of diabetes (years)	0 to 3	4 to 6	7 to 9	More than 10	Total
N	65	25	32	115	237
Gender (M/F)	28/37*	12/13	18/14	73/42	131/106
Age at diabetes diagnosis (years)	55.28±13.74	53.77±10.48	50.66±8.75	46.90±9.50**	50.39±11.28
Age at insulin initiation (years)	56.08±13.55	58.89±10.24	58.44±9.06	63.51±8.89**	60.49±10.80
Insulin initiation during hospitalization (%)	63.6**	56.0	56.3	58.2	58.5
History of obesity (%)	16.9	36.0*	11.1	22.6	21.7
HbA1c at insulin initiation (%)	11.52±2.34**	10.36±1.27	10.05±1.84	9.79±1.75	10.35±2.01

*p<0.05 compared with other 3 groups, **p<0.01 compared with other 3 groups (ANOVA and post-hoc Tukey analyses).
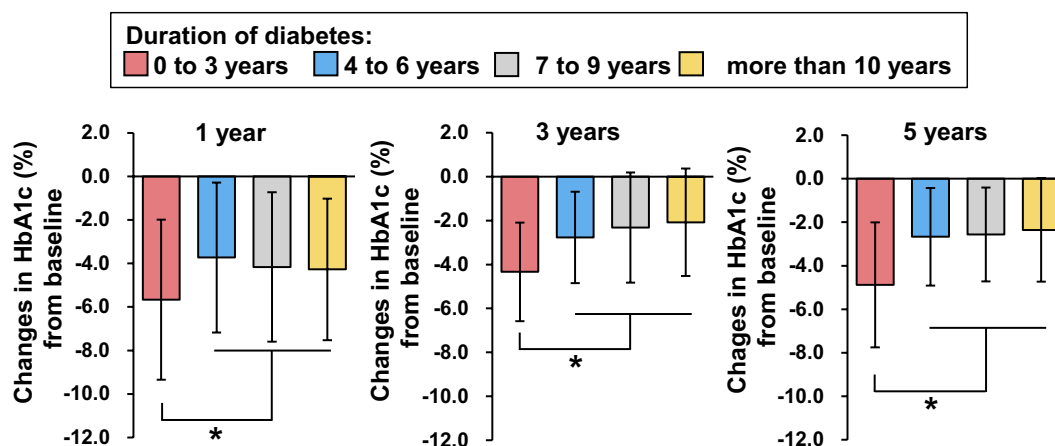
Figure 1.   Changes in HbA1c levels in patients with type 2 diabetes with a diabetes duration of ≤3 years, 4 to 6 years, 7 to 9 years, or ≥10 years at the time of insulin initiation. Data represent the mean±SD. *p≤0.01 (ANOVA and post-hoc Tukey analyses).

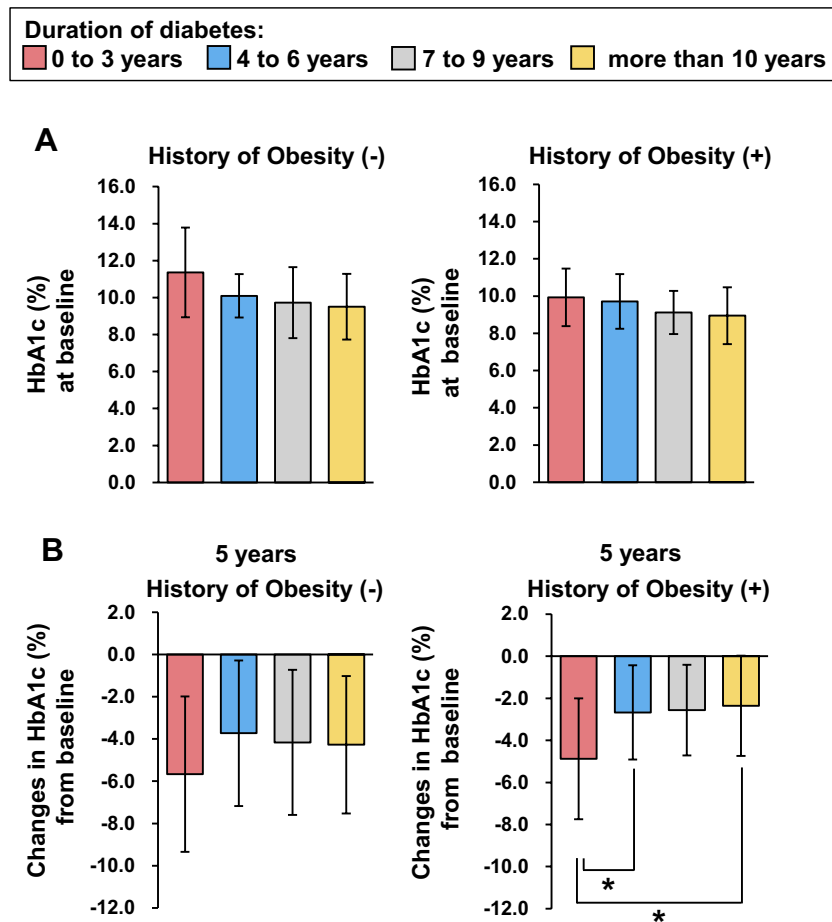**Table 2.   HbA1c Levels at 1, 3, or 5 Years after Insulin Initiation.**

Duration of diabetes (years)	0 to 3	4 to 6	7 to 9	More than 10
HbA1c (%) at 1 year	7.10±1.49	7.96±1.33	7.92±1.39	7.53±1.11
HbA1c (%) at 3 year	7.17±1.19	7.80±1.30	7.73±1.40	7.46±1.17
HbA1c (%) at 5 year	7.19±1.27	7.88±1.80	7.76±1.21	7.55±1.23

0.05) than the other 3 groups. We next analyzed the changes in the HbA1c level at 1, 3, and 5 years after insulin initiation. The patients who started insulin injections ≤3 years after their diabetes diagnosis had significantly larger reductions in HbA1c at all 3 time points (-4.52±2.61% at 1 year, p<0.01; -4.34±2.24% at 3 years, p<0.01; and -4.88±2.87% at 5 years, p<0.01), than all the other duration groups (Fig. 1 and Table 2).
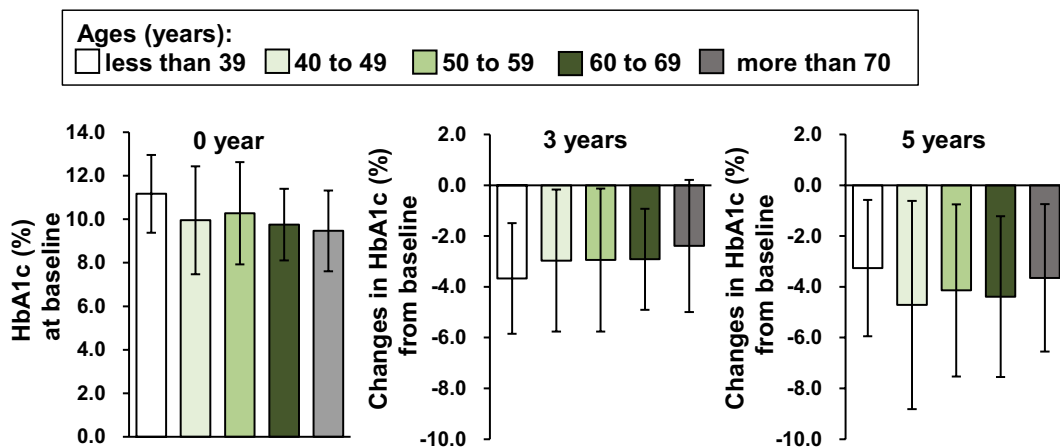
The duration of diabetes and the HbA1c levels before insulin initiation did not differ markedly according to the history of obesity (Fig. 2A). The reduction in HbA1c was, however, greater among patients with a diabetes duration of ≤3 years than in those with a duration of 4 to 6 years or ≥10 years, only among patients with a history of obesity at 5 years after insulin initiation (Fig. 2B). The subjects who had a BMI>25 at the initiation of insulin also showed a similar tendency (data not shown).

We next divided the patients into 5 groups according to age: <40 years old (n=13), 40 to 49 years old (n=21), 50 to 59 years old (n=66), 60 to 69 years old (n=87), and ≥70 years old (n=44). There were no significant differences in the changes in the HbA1c levels among these age groups at 1, 3, or 5 years after insulin initiation (Fig. 3).

Next, the patients were divided into 4 groups according to the frequency of insulin injections per day: once (n=33), twice (n=9), 3 times (n=11), or 4 times (n=93). The decrease in HbA1c was greater in the group with 4 daily insulin injections (-4.16±2.21% at 3 years and -4.02±2.50% at 5 years) than in the group with 3 daily injections at 3 years (-1.77±3.84%, p<0.01) and the group with once-daily injection at 3 and 5 years (-1.23±2.56% at 3 years, p<0.01; and -1.08±1.48% at 5 years, p<0.01) (Fig. 4A). In the group with once-daily insulin injections, the HbA1c level before and after insulin initiation did not differ significantly accord-

Figure 2. Effects of obesity history on HbA1c levels at baseline (A) and on changes in HbA1c levels at 5 years after insulin initiation (B) in patients with type 2 diabetes with a diabetes duration of ≤3 years, 4 to 6 years, 7 to 9 years, or ≥10 years at the time of insulin initiation. Data represent the mean±SD. *$p \leq 0.05$ (ANOVA and post-hoc Tukey analyses).
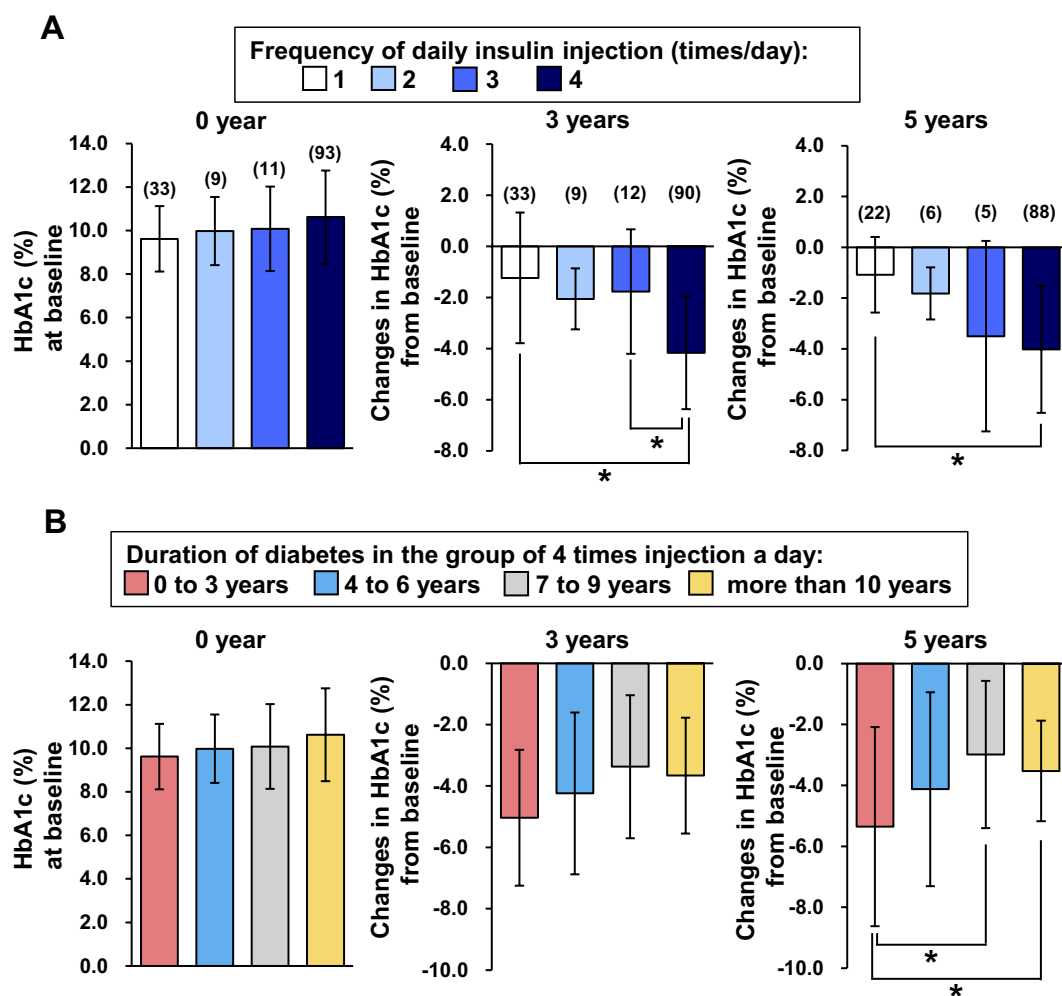

Figure 3. Changes in HbA1c levels in patients with type 2 diabetes who are<40, 40 to 49, 50 to 59, 60 to 69, or ≥70 years old. Data represent the mean±SD. *$p \leq 0.05$ (ANOVA and post-hoc Tukey analyses).

ing to the duration of diabetes. However, in the group with 4 daily injections, the reduction in the HbA1c level was greater in patients with a diabetes duration of ≤3 years (-5.35±2.21%) than in those with a duration of 7 to 9 years or ≥10 years at 5 years after the start of insulin injections (Fig. 4B).

Hospitalized patients showed greater improvement in their glycemic control than outpatients at 1 and 3 years after in-

Figure 4. (A) Changes in HbA1c levels in patients with type 2 diabetes who received insulin injections once, twice, three times, or four times daily. The number of subjects in each group is described on the bars. (B) Changes in HbA1c levels in patients with type 2 diabetes receiving 4 insulin injections daily and who had a diabetes duration of ≤3 years, 4 to 6 years, 7 to 9 years, or ≥10 years at the time of insulin initiation. Data represent the mean±SD. *p≤0.05 (ANOVA and post-hoc Tukey analyses).

sulin initiation (Fig. 5). We also analyzed the HbA1c levels before the initiation of insulin with the changes in the HbA1c level at 1, 3, and 5 years after insulin initiation. There were significant inverse correlations between the HbA1c level at baseline and the reduction in the HbA1c levels (r= -0.707, p<0.001 at 1 year; r=-0.792, p<0.001 at 3 years; r= -0.393, p<0.001 at 5 years).

Discussion

In this study, we showed the effects of the timing of insulin initiation on glycemic control in Japanese patients with type 2 diabetes using retrospective medical records in terms of several clinical aspects, including the disease duration, age, and frequency of insulin injection.

The ORIGIN, EASIE, EARLY, and GLORY studies previously demonstrated that earlier insulin use in the treatment of diabetes resulted in the improvement of glycemic control and a reduction in hypoglycemic events (9-12). In the pre-

sent study, we investigated the effects of the timing of insulin initiation on glycemic control at 3 or 5 years in Japanese patients with type 2 diabetes using in- and out-patient medical records. We described the changes in the HbA1c levels after insulin initiation in terms of the duration of diabetes at insulin initiation, the history of obesity, patient age, and the frequency of daily insulin injections.

A previous report showed that a longer diabetes duration and a lower age at baseline were associated with a shorter time to the initiation of insulin (13). Patients in the present study with a diabetes duration of ≥10 years had an older age at the time of insulin initiation, despite having a younger age at the time of their diabetes diagnosis, than those in other age groups. These results might reflect the earlier initiation of insulin injection to improve glycemic control that has been adopted by physicians caring for diabetes patients in recent years, based on recent evidence (9-12). Interestingly, the patients who had been diagnosed for ≤3 years at the time of insulin initiation had a significantly greater re-
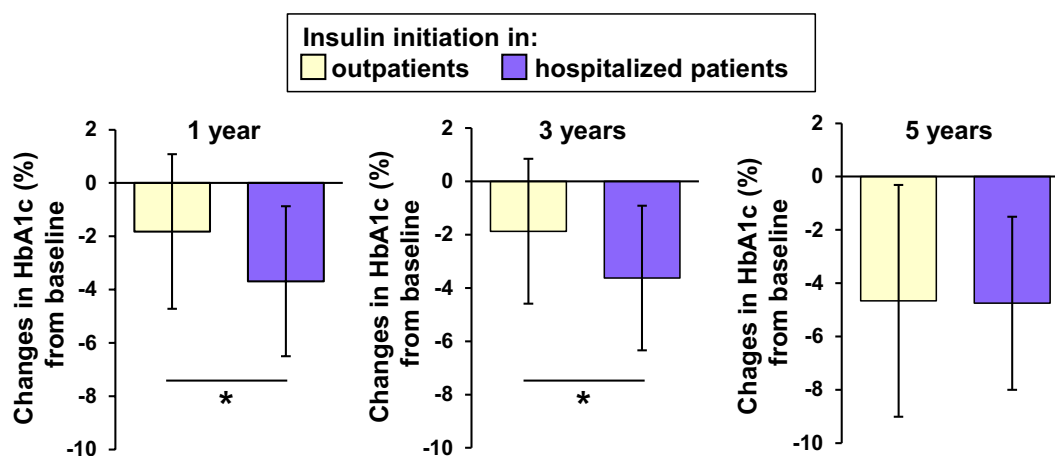
Figure 5. Changes in HbA1c levels in patients with type 2 diabetes who started insulin injections in the outpatient or hospitalized setting. Data represent the mean±SD. *p≤0.05 (Student's t-test).

duction in HbA1c at 1, 3 and 5 years of insulin injection than those with a longer duration of diabetes. A higher HbA1c level before insulin initiation in patients with a diabetes duration of ≤3 years may have contributed to better glycemic control.

Because the subjects who started insulin injections ≤3 years after their diagnosis had a higher frequency of insulin initiation during hospitalization, hospitalized patients may have maintained better glycemic control than outpatients due to receiving adequate instructions regarding insulin injection and education on diabetes care. Furthermore, a hospitalized setting may overcome the difficulty in initiating insulin injections in terms of clinical inertia. Previous studies have also indicated that hospitalization is effective for glycemic control and treatment satisfaction (14-16). The pancreatic β-cell function is known to decline gradually during the course of diabetes. Since the difference in glycemic control persisted for 5 years, subjects with a diabetes duration of ≤3 years at the time of insulin initiation might retain a secretory capacity for insulin, and this capacity may be preserved through supplementation with exogenous insulin. This hypothesis may warrant additional research evaluating the intrinsic capacity to secrete insulin before and after insulin initiation. In addition, a history of obesity seemed to be an important factor for reducing HbA1c in patients who have been using insulin for ≤3 years. This might also reflect the contribution of diabetes care education to glycemic control in obese patients.

There were no significant changes in the decrease in HbA1c after insulin initiation among the different age groups. Diabetes is a well-known risk factor for cognitive dysfunction, and proper self-injection is difficult for patients with dementia. In the present study, only a few patients had dementia. A further study, including a larger number of older subjects, will be required in order to assess the effects of aging on the maintenance of glycemic control by insulin injection. In our study, we also showed that four insulin injections daily lowered the HbA1c level compared with once- or three-times-daily injections. Since the average HbA1c level was 10.3%, most people started insulin injections because their blood glucose levels were very poorly controlled. In patients with poor glycemic control, in addition to basal insulin, post-prandial insulin is required to improve hyperglycemia. Therefore, multiple daily insulin injections might promote better HbA1c levels.

One limitation of this study was its retrospective design. In addition, only 237 patients were enrolled, and there was no control group. Furthermore, exact information regarding drugs and other co-factors throughout the long-term follow-up period were not included in some medical records. In this study, we did not investigate the contribution of the intrinsic insulin secretion capacity, although serum C-peptide levels influence glycemic control by insulin injection and their outcome (17, 18).

In summary, the results of our investigation suggested that earlier insulin initiation is crucial for sustainable glycemic control in Japanese patients with type 2 diabetes, particularly in subjects with a history of obesity or multiple daily insulin injections. A hospitalized setting might be useful for the initiation of insulin therapy to avoid clinical inertia and promote better glycemic control. A prospective study is needed in order to determine whether or not a causal relationship exists between the duration of diabetes and glycemic control after insulin initiation.

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