

Intensive insulin therapy for Japanese patients with type 2 diabetes mellitus - Results in the patients from single hospital -

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Objective: We investigated the clinical characteristics of intensive insulin therapy in Japanese type 2 diabetes patients who commenced intensive insulin therapy during the in-hospital diabetes education program at Tokai university hospital.

Methods: 81 type 2 diabetes patients who received intensive insulin therapy and in-hospital diabetes education program were examined their clinical features.

Results: Intensive insulin therapy maintained HbA_{1c} below 7% at all time points during the 2-year follow-up, though it was not necessary to increase the insulin dose, thus highlighting the clinical utility of the therapy in preventing diabetic complications. Insulin therapy could be withdrawn from more than 25% of patients. The diabetic morbid period was shorter and urinary C-peptide level at admission was higher in patients of the withdrawal group than those of the non-withdrawal group, suggesting that patients with well maintained pancreatic β cell reserve could be withdrawn from insulin therapy.

Conclusions: Based on our results of the efficacy of strict glycemic control for preventing the development and progression of diabetic complications, we recommend early introduction of intensive insulin therapy to achieve better glycemic control.

Key words: Type 2 diabetes, intensive insulin therapy, Japanese

INTRODUCTION

Recent studies including the Diabetes Control and Complication Trial (DCTT) [1], United Kingdom Prospective Diabetes Study (UKPDS) [2], and Kumamoto Study [3] have revealed that strict glycemic control prevents the development and progression of diabetic microvascular complications. Although the DCTT and Kumamoto Study used intensive insulin therapy as a strict glycemic control, few studies have examined the efficacy of and adverse reactions to the therapy in Japanese type 2 diabetes patients. In the present study, we investigated the clinical characteristics of intensive insulin therapy in Japanese type 2 diabetes patients who commenced intensive insulin therapy during the in-hospital diabetes education program at our hospital.

PATIENTS AND METHODS

The study subjects were 108 type 2 diabetes patients who started the in-hospital diabetes education program and intensive insulin therapy at Tokai University Hospital from 1997 to 2003. Then 81 patients who could be followed for two years after discharge were examined for gender, age, diabetes duration, body mass index (BMI), glycated hemoglobin (HbA_{1c}) and urinary C-peptide at admission and daily dose of insulin at discharge. They were also examined for HbA_{1c}, daily insulin dose, and body weight during the two-

year follow-up period.

Intensive insulin therapy was defined as the "injection of regular insulin or fast-acting human insulin analogs before each meal and neutral protamine Hagedorn (NPH) insulin at bedtime to compensate for the loss of insulin as basic and additional doses, respectively, and diabetes education program that includes self-monitoring of blood glucose (SMBG) and once-monthly hospital visits for strict glycemic control."

The 81 patients were classified into two groups; those in whom insulin therapy could be withdrawn during the follow-up period (withdrawal group) or those who could not (non-withdrawal group). We then compared the clinical characteristics at admission of the two groups. Withdrawal from insulin therapy was defined as "reduction of insulin dose during the follow-up period on an outpatient basis, followed by replacement with diet therapy or oral medicines."

Data were expressed as mean \pm SD. Differences between groups were examined for statistical significance by the Mann-Whitney U test and Wilcoxon signed-rank test. A *P* value of <0.05 was considered statistically significant.

RESULTS

The subjects consisted of 62 males and 19 females with a mean age of 53.9 ± 11.7 years at admission and BMI of 23.5 ± 3.7 kg/m². The estimated duration of diabetes was 11.5 ± 8.7 years. Laboratory findings

Table 1. Comparison of clinical characteristics between withdrawal group and non-withdrawal group

	Withdrawal group (n=21)	Non-withdrawal group (n=60)	p-value
Gender (M/F)	15/6	47/13	N.S.(0.5204)
Age (y/o)	53.2±11.9	55.9±11.4	N.S.(0.4471)
Duration (years)	7.1±6.3*	13.0±8.3	0.0009
Body mass index (kg/m ²)	23.7±3.1	23.8±4.2	N.S.(0.7422)
HbA _{1c} (%)	9.6±1.7	8.9±1.6	N.S.(0.0726)
Urinary C-peptide (μg/day)	93.3±48.1	71.2±42.1	N.S.(0.0771)
Daily insulin dose at discharge(U/day)	22.9±9.6	24.8±8.6	N.S.(0.2585)

Data are expressed as mean±S.D., N.S.; not significant, * $p<0.05$ vs non-withdrawal group

at admission included HbA_{1c} of $9.1 \pm 1.7\%$, urinary C-peptide of 77.7 ± 44.7 μg/day. Table 1 compares the clinical features of patients of the withdrawal group and those of the non-withdrawal group. There was a significant difference in the duration of diabetes between the two groups.

Fig. 1 shows changes in HbA_{1c}, daily insulin dose and body weight during the two-year follow-up period in all patients. HbA_{1c} remained below 7% during the follow-up period, including $6.6 \pm 1.1\%$ at six months, $6.7 \pm 1.0\%$ at one year, and $6.9 \pm 1.1\%$ at two years, as compared with $9.1 \pm 1.7\%$ at admission. The daily insulin dose during the two-year follow-up period in all patients was almost constant from discharge through the follow-up period: 24.3 ± 8.8 U/day at discharge, 21.7 ± 12.7 U/day at six months, 21.5 ± 15.1 U/day at one year, and 22.4 ± 16.1 U/day at two years. No significant change in body weight was during the first year after discharge; however, there were significant increases in body weight after one year.

Eleven patients could be successfully withdrawn from insulin therapy at six months after discharge and eight from six months to one year after discharge, while only two patients could be withdrawn from one to two years. This indicates that the majority of patients could be withdrawn from the therapy during the first year after discharge. With regard to comparison of clinical features of the withdrawal and non-withdrawal groups, patients of the withdrawal group had a significantly shorter estimated duration of diabetes, and had a trend of higher HbA_{1c} and urinary C-peptide levels at admission than the non-withdrawal group. There was no significant difference in the gender ratio, age, and BMI, HbA_{1c} and urinary C-peptide at admission and daily insulin dose at discharge between the two groups (Table 1). Fig. 2 shows changes in HbA_{1c},

daily insulin dose and body weight during the two-year follow-up period in withdrawal group and non-withdrawal group. HbA_{1c} remained below 6.5% during the follow-up period in withdrawal group. The daily insulin dose during the two-year follow-up period in withdrawal group was significantly decrease, on the other hand, the daily insulin dose non-withdrawal group was tend to increase from discharge through the follow-up period: 24.8 ± 8.6 U/day at discharge, 25.3 ± 11.6 U/day at six months, 26.9 ± 12.7 U/day at one year, and 28.9 ± 12.8 U/day at two years. No significant change in body weight was during the first year after discharge; however, there were significant increases in body weight after one year in non-withdrawal group and there was no significant body weight increase in withdrawal group. Furthermore, no serious hypoglycemia requiring hospital admission occurred during the observation period.

DISCUSSION

Insulin was originally used for saving life from acute complications when it was discovered in 1921. With the subsequent development of insulin preparations, the target of insulin therapy was changed to strict glycemic control intended for preventing the development and progression of chronic complications. In 1990's, large intervention studies for types 1 or 2 diabetes in Western countries, such as DCCT [1] and UKPDS [2], demonstrated that strict glycemic control is important for preventing the development and progression of chronic complications of both types 1 and 2 diabetes. Furthermore, the Kumamoto study [3] of Japanese type 2 diabetes patients showed that intensive insulin therapy significantly reduced the risk of microvascular complications. Currently, strict glycemic control is recommended in order to keep HbA_{1c} below 7%

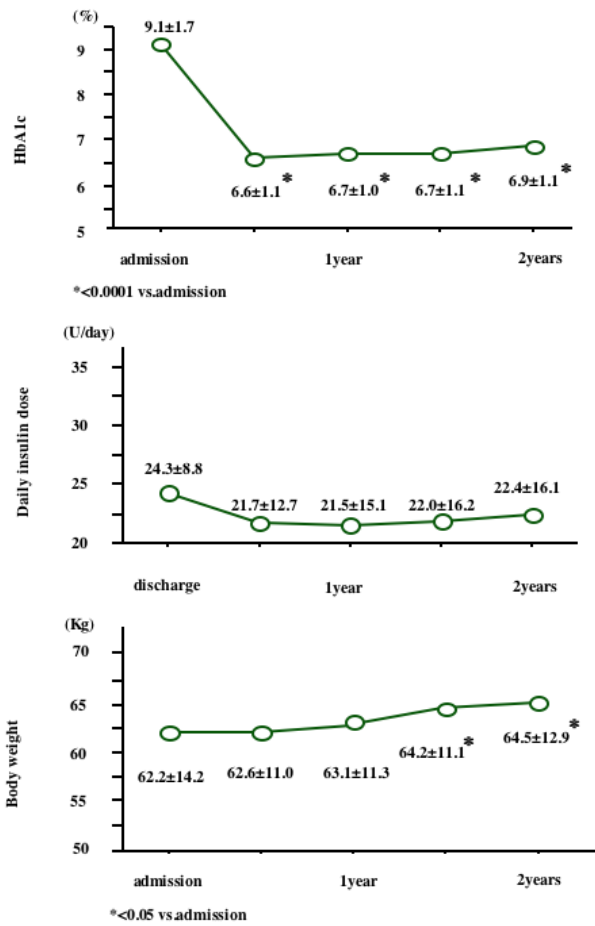


Fig. 1. Serial changes in HbA_{1c}, daily insulin dose and body weight after discharge in all patients.

to prevent the development and progression of diabetic microangiopathy. In our hospital, intensive insulin therapy was introduced around 1995, and achieving a strict glycemic control has become possible. We have reported the comparison between the intensive insulin therapy and the conventional therapy in the past [4]. These two groups were received the same diabetic education program, however, it reported the intensive insulin therapy to be excellent for the glycemic control and the insulin withdrawal rate. Therefore, we assumed the further examination of the efficacy of the intensive insulin therapy for the research purpose.

In the present study, intensive insulin therapy maintained HbA_{1c} below 7% at all time points examined during the two-year follow-up period. Daily insulin dose was almost constant during the same period in all patients; i. e., it was not necessary to increase insulin dose to keep HbA_{1c} low. However, daily insulin dose of non-withdrawal group was slightly increased and there was a significant increase at two years after discharge. These results indicate that intensive insulin therapy seems to maintain strict glycemic control. It also indicate that patients who could not withdraw from insulin therapy need an appropriate education and care during long term follow up to avoid increasing insulin as same as the conventional therapy group.

With regard to body weight change after the

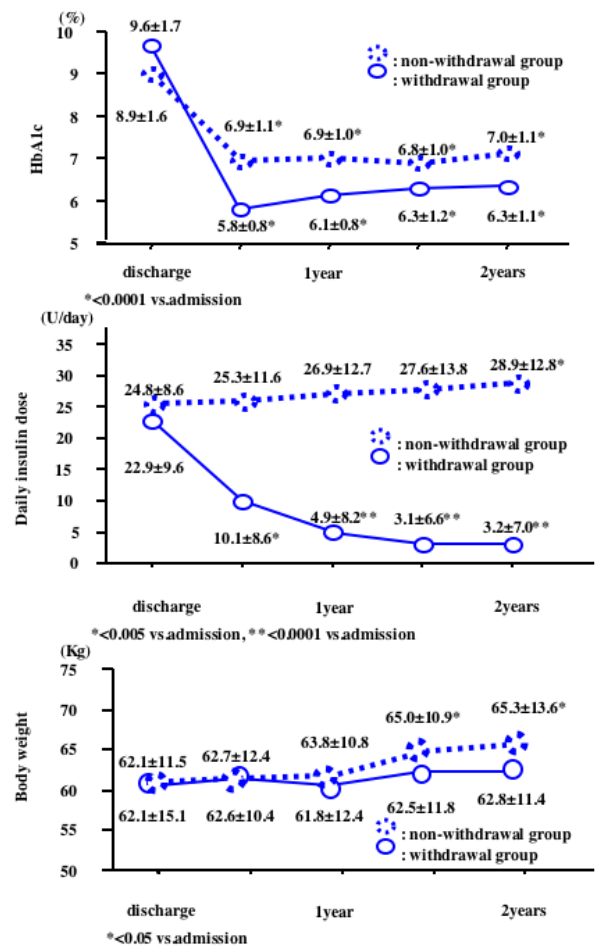


Fig. 2. Serial changes in HbA_{1c}, daily insulin dose and body weight after discharge in withdrawal group and non-withdrawal group.

introduction of intensive insulin therapy, DCCT [1] reported that the number of patients who experienced increased body weight above 120% of standard body weight in the intensive insulin therapy group was 1.4 times as large as that in the conventional therapy group, while the Kumamoto study [3] reported that none of the patients in the intensive insulin and conventional therapy groups experienced increased body weight. The two intervention studies cannot be directly compared because of differences in racial structure, study environment, and types of diabetes (type 1 or 2). The change in body weight identified in the present study is inconsistent with the finding of Kumamoto study since a significant increase in body weight was observed after one-year follow-up. From our study, body weight in the intensive insulin therapy group was constant. The efficacy of an appropriate outpatient care interval and an appropriate diet therapy or exercise program were thought as a cause. On the other hand, diet failure patients were often seen in the non-withdrawal patients. Our results suggest that adequate diet therapy and exercise are required in addition to intensive insulin therapy to achieve standard body weight, especially for non-withdrawal patients.

In the present study, withdrawal from insulin therapy could be achieved in approximately 26% of the patients. Patients of the withdrawal group were charac-

Table 2. Typical cases of withdrawal group patients

	Case 1	Case 2
Urinary C-peptide ($\mu\text{g}/\text{day}$)	78.2	157.0
HbA _{1c} at admission (%)	12.6	12.3
HbA _{1c} at withdraw (%)	5.7	5.1
Daily insulin dose change (U/day)	27→0	24→0

terized by short diabetic morbid period. Furthermore, they had a trend of high urinary C-peptide and high HbA_{1c} at admission compared with those of the non-withdrawal group. In other words, short diabetic morbid period patients with high urinary C-peptide and high HbA_{1c}, i. e., glucotoxicity and insulin resistance state patients may have maintained pancreatic β cell function. This suggests that patients with acceptably maintained pancreatic β cell reserve can be withdrawn from insulin therapy, as reported in earlier studies [5–7]. Furthermore, the fact that withdrawal from insulin therapy was mainly achievable during the first year after discharge suggests that withdrawal from the therapy beyond one year of commencement may be difficult. Li *et al.* reported that intensive insulin therapy could induce long-term glycemic control and the improvement of β cell function [6]. We also have the typical cases that we had experienced, and typical two cases were presented in Table 2. In summary, intensive insulin therapy is expected to be effective for, and withdrawal from the therapy is expected, in patients with well-maintained pancreatic β cells probably because glucose toxicity is eliminated in such patients. Since HbA_{1c} at admission tended to be higher in the withdrawal group, early introduction of insulin therapy may increase the possibility of withdrawal even in poorly controlled patients.

Intensive insulin therapy has been reported to cause several problems, such as frequent hypoglycemia and complex control procedure. DCCT [1] indicated that the incidence of serious hypoglycemia was increased with stricter glycemic control, reporting serious hypoglycemia as an adverse reaction to intensive insulin therapy. DCCT also reported that intensive insulin therapy increased the likelihood of severe hypoglycemia requiring care by others by 3.3 times compared with conventional therapy, while the Kumamoto study [3] reported no severe hypoglycemia in the patients treated with intensive insulin therapy. The risk of severe hypoglycemia is a major barrier to initiation of insulin treatment [8]. Unlike DCCT [1] of type 1 diabetes patients, none of the type 2 diabetics of the present study developed serious hypoglycemia requiring admission during the follow-up period. Our result revealed that intensive insulin therapy could be used safely for a better glycemic control in type 2 patients

with no increase in hypoglycemia, under a thorough understanding of risk factors [8–10]. Although intensive insulin therapy tends to be clinically avoided because of repeated injections and complex control procedure, none of the patients of the present study gave up the therapy during the follow-up period (no patients switched from intensive insulin therapy to conventional therapy consisting of insulin injections of once or twice daily).

In conclusion, the present study confirmed that intensive insulin therapy for Japanese type 2 diabetes patients maintained low levels of HbA_{1c} without markedly changing insulin dose, demonstrating the utility of the therapy for strict glycemic control. More than 25% of patients could be withdrawn from the therapy. Based on our results of the efficacy of strict glycemic control for preventing the development and progression of diabetic complications, we recommend early introduction of intensive insulin therapy to achieve better glycemic control.

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