

Effectiveness of Basal-supported Oral Therapy (BOT) Using Insulin Glargine in Patients with Poorly Controlled Type 2 Diabetes

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Objective: To determine the clinical usefulness of basal-supported oral therapy (BOT) using insulin glargine in Japanese patients with type 2 diabetes.

Methods: We compared HbA1c levels, body weight, and insulin doses before the introduction of BOT and in the final month of the observation period in 122 patients with type 2 diabetes who received BOT with insulin glargine between October 2007 and July 2009. To exclude the possible effects of seasonal changes in glycemic control, 57 of the 122 patients were followed-up for one year and examined for changes in HbA1c levels, body weight, and insulin dose.

Results: Examination of all cases (n = 122) showed a significant decrease in HbA1c (before BOT: 8.7 ± 1.8 , after: $7.1 \pm 1.1\%$), but no significant change in body weight (before: 63.1 ± 16.1 , after: 63.8 ± 17.0 kg). The mean observation period was 10.5 ± 6.4 months. Insulin doses were significantly increased during the study. HbA1c levels improved significantly in patients on non-insulin-secreting drugs (biguanide, α -glucosidase inhibitor and thiazolidine derivatives) than those on insulin-secreting drugs (SU agents and glinides).

Conclusion: BOT with insulin glargine is a useful strategy that can achieve good glycemic control in clinical practice without causing serious hypoglycemia. The introduction of BOT before exhaustion of pancreatic β cells may increase its effectiveness.

Key words: BOT, Type 2 Diabetes, Insulin glargine

INTRODUCTION

Early introduction of insulin therapy in the treatment of type 2 diabetes has become common in recent years to prevent glucose toxicity and protect pancreatic β cells.

Recent years have seen changes in the Japanese social structure, with increased numbers of elderly and/or those who live alone. This has increased the proportion of patients on oral hypoglycemic agents, although insulin therapy would be preferable. In basal-supported oral therapy (BOT), long-acting insulin is added to oral hypoglycemic agents, without any reduction or discontinuation of the oral agents. While many overseas studies have demonstrated the usefulness of BOT [1-7], only a few such studies have been conducted in Japan. Furthermore, Japanese patients with type 2 diabetes have a lower capacity to secrete insulin than patients of western country [8]. Thus, BOT therapy may be beneficial with regard to preservation for exhausted β cell function. Insulin glargine, a long-acting insulin analogue, does not show a definite peak effect but rather a sustained effect that lasts for nearly 24 hours. Therefore, it is a potentially the best agent to use in BOT.

The purpose of this study was to assess the therapeutic effects of BOT, in terms of improvement of

glycemic control and use of concomitant therapies [e.g., insulin glargine and oral hypoglycemic agents, in particular sulfonylureas (SUs)] in Japanese patients with type 2 diabetes.

PATIENTS AND METHODS

Subjects and Study Protocol

This research project was conducted as an observational study. This retrospective study included 122 patients with type 2 diabetes who received BOT with insulin glargine at the Department of Nephrology and Metabolism Outpatient Clinic at the Tokai University Hospital between October 2007 and July 2009. BOT was introduced for the patients that HbA1c levels could not achieve 6.9% even if they used oral hypoglycemic drugs. Data were retrieved on HbA1c levels, body weight, and insulin doses before the introduction of BOT and in the final month of the observation period. Among the 122 patients, 57 could be followed up for more than 12 months after the introduction of BOT. To exclude the possibility of seasonal changes in glycemic control, we selected these 57 patients and further examined HbA1c and fasting blood glucose (FBS) levels, body weight, and insulin dose at 6, 9 and 12 months after the introduction of BOT. These 57 patients were further surveyed for the use of concomitant oral medications and doses of each class of oral

Table 1 Clinical characteristics of patients before the introduction of BOT.

	All Cases (n = 122)	12-months follow-up group (n = 57)
Gender (M/F)	79/43	38/19
Age (years)	65.7 ± 11.7	66.1 ± 11.3
Body weight (kg)	63.1 ± 16.1	65.5 ± 18.0
Body mass index (kg/m ²)	24.3 ± 4.5	25.7 ± 4.9
HbA1c (%)	8.7 ± 1.8	8.6 ± 1.8
Disease duration (years)	N.R.	14.7 ± 11.4
Follow-up period (months)	10.5 ± 6.4	N.R.
Retinopathy (yes/no/unknown)	N.D.	21/21/15
Nephropathy (yes/no/unknown)	N.D.	17/18/22

Data are mean ± S.D. or number of patients
N.R.: not recorded, N.D.: not done

medications used before and after the introduction of BOT. Subjects on oral hypoglycemic drugs were categorized into those on SU alone or in combination with other medications (SU group), those on glinide alone or in combination with other medications (glinide group), and those on neither SU nor glinide (other drug group). For comparison of clinical parameters according to the SU dose, the doses of glimepiride ≥ 4 mg/day, glibenclamide ≥ 2.5 mg/day, and gliclazide ≥ 40 mg/day were defined as high-dose therapy, and lower dosages as low-dose therapy. In almost all cases, the initial dose of insulin glargine during the observation period was 4 U/day, and the maximum dose increase at one time was 4 U. Guidance on self-monitoring of blood glucose (SMBG) was provided to all of the patients, and most of them brought their SMBG records when they visited the outpatient clinic. Outpatient review was continued every 4–8 weeks so that safety adjustment of insulin glargine and glycemic control could be maintained. Changes in the dosages of oral hypoglycemic agents were at the discretion of the treating physicians.

All patients were checked for retinopathy and nephropathy based on the data available in the medical records. Retinopathy was considered present if simple retinopathy or a more severe disorder had been diagnosed by an ophthalmologist. Nephropathy was defined as urinary protein of trace or over according to the dipstick test, or urinary albumin-to-creatinine ratio (ACR) of > 30 mg/g Cr.

Statistical analysis and ethical considerations

Results were expressed as mean ± standard deviation (SD). Data were analyzed using the Wilcoxon signed rank sum test and Mann-Whitney U test. A P value less than 0.05 denoted the presence of significant difference. The study protocol was approved by the Human Ethics Review Committee of Tokai University and a signed consent form was obtained from each subject. HbA1c [%] value is calculated by the formula $HbA1c[\%] = HbA1c [Japan Diabetes Society (JDS) [\%]] + 0.4\%$, considering the rational expression of HbA1c [JDS] [%] measured by the previous Japanese standard substance and measurement methods and HbA1c [National Glycohemoglobin Standardization Program] [9].

RESULTS

Table 1 summarizes the background characteristics of the 122 subjects. There were no drop out cases during observation period. The mean observation period was 10.5 ± 6.4 months. Table 1 also lists the characteristics of the 57 subjects who were followed for 12 months. The mean estimated duration of the disease was 14.7 ± 11.4 years. The historical record of complications showed that retinopathy was diagnosed in 21 patients and confirmed to be negative in 21, while the status was not recorded in 15. Nephropathy was diagnosed in 17 patients, absent in 18 and not recorded in 22. The other medications used by the 57 patients before the introduction of BOT were SU agents (n = 29), glinides (n = 12), and others (n = 16), with 21 taking α -glucosidase inhibitors, 20 biguanides, and 12 thiazolidines. The SU agents used were glimepirides (n = 21), glibenclamide (n = 5), and gliclazides (n = 3).

We surveyed the dosages of oral hypoglycemic agents in the follow-up group. There were no significant differences in subject background characteristics based on the class of oral hypoglycemic agent used. There were no increases in dosage, or addition, of oral hypoglycemic agents during the observation period. The mean dosage of each SU agent was lower at 12 months after the introduction of BOT (glimepiride: before, 2.9 ± 1.8 ; after, 1.9 ± 1.6 . glibenclamide: before, 6.0 ± 2.8 ; after 0.0 ± 0.0 . Gliclazide: before, 66.7 ± 11.6 ; after 50.0 ± 42.4 mg/day). The mean dosages of glinides and other oral hypoglycemic agents were not changed after the introduction of BOT.

All subjects underwent examination and various investigations before the introduction of BOT and in the final month of the observation period. HbA1c and FBS decreased significantly after the introduction of BOT (HbA1c: before 8.7 ± 1.8 , after: $7.1 \pm 1.1\%$; FBS: before 163.7 ± 44.8 , after 111.7 ± 22.7 mg/dl). However, no significant changes were noted in body weight (before: 63.1 ± 16.1 , after: 63.8 ± 17.0 kg). The dose of insulin was significantly increased (Fig. 1a-c).

In the follow-up group, HbA1c decreased significantly after the introduction of BOT (before: 8.6 ± 1.8 , 6 months: 7.1 ± 1.0 , 12 months: $7.2 \pm 0.8\%$), although the difference between the values at 6 and 12 months was not significant. No significant change was observed in body weight after BOT (before: 65.5 ± 18.0 ,

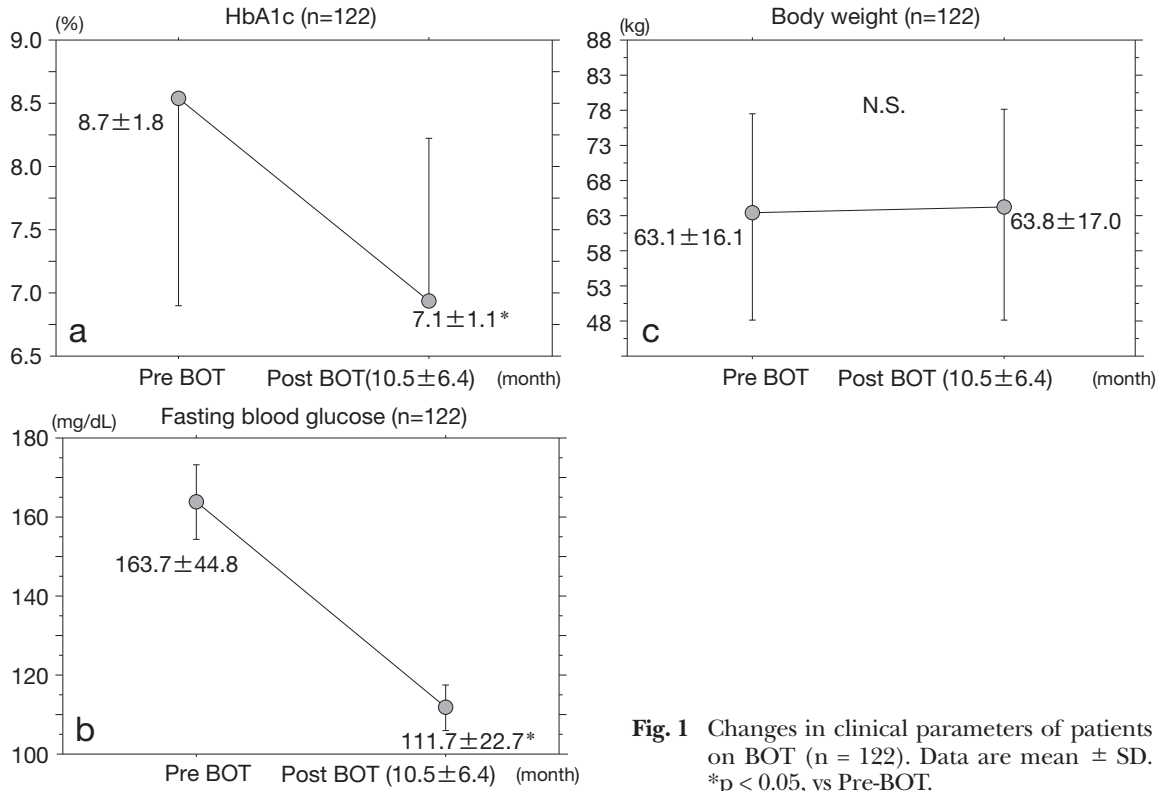


Fig. 1 Changes in clinical parameters of patients on BOT (n = 122). Data are mean ± SD. *p < 0.05, vs Pre-BOT.

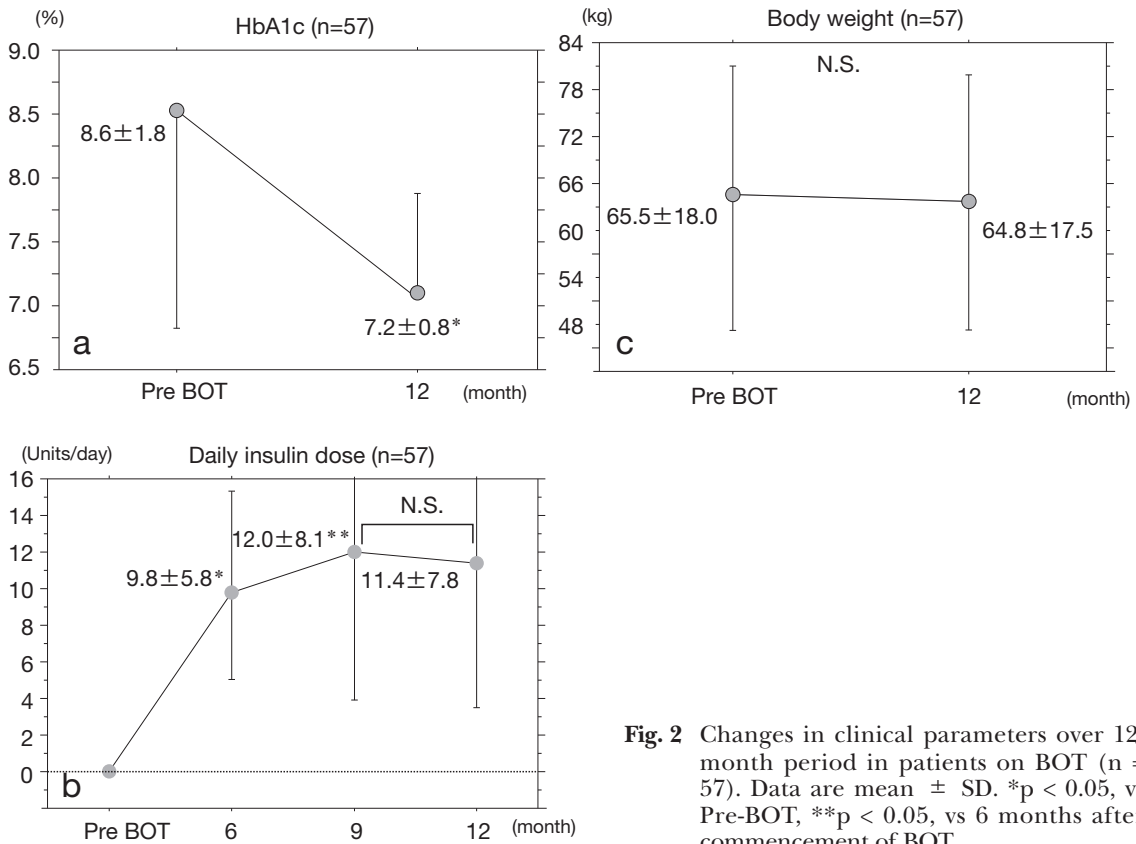


Fig. 2 Changes in clinical parameters over 12-month period in patients on BOT (n = 57). Data are mean ± SD. *p < 0.05, vs Pre-BOT, **p < 0.05, vs 6 months after commencement of BOT.

6 months: 63.9 ± 17.2, 12 months: 64.8 ± 17.5 kg). The dose of insulin increased significantly after BOT (before: 0, 6 months: 9.8 ± 5.8, 9 months: 12.0 ± 8.1, 12 months: 11.4 ± 7.8 U) (Fig. 2a-c). No hypoglycemic events requiring hospitalization were reported during

the observation period.

The therapeutic effects of SU agents and glinides, which have insulin-secreting effects, and those of other agents (non-insulin-secreting drugs) were compared. Fasting blood glucose significantly improved after

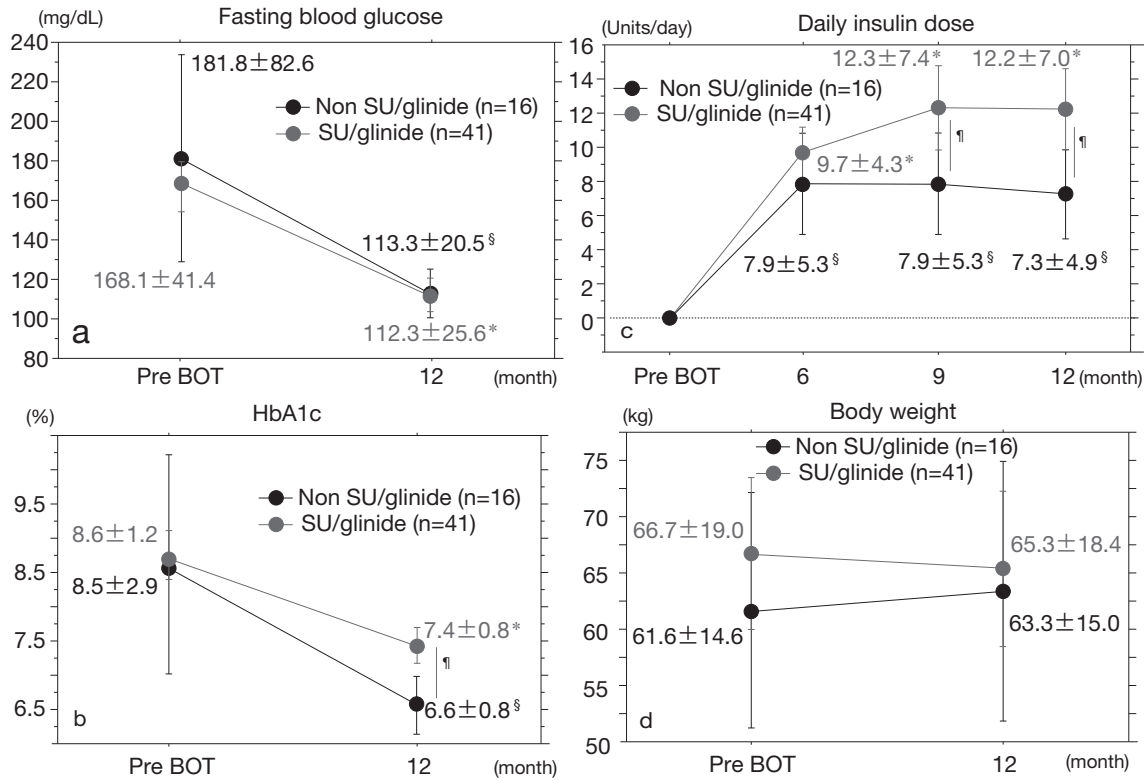


Fig. 3 Comparison of changes in clinical parameters over 12 months of patients treated with SU/glinide and non-SU/glinide oral hypoglycemic agents ($n = 57$). Data are mean \pm SD. ¶ $p < 0.05$ vs SU/glinide group, § $p < 0.05$, vs Pre-BOT, * $p < 0.05$, vs Pre-BOT.

the introduction of BOT in patients on both types of medications, with no significant difference between the two groups. However, HbA1c levels improved significantly in patients on the non-insulin-secreting drugs compared with those on the insulin-secreting drugs. In patients on the non-insulin-secreting drugs, the daily dose of insulin was also significantly lower from 9 months after the introduction of BOT (Fig. 3a-d).

Finally, we compared the clinical parameters of patients on high-dose SU (glimepiride ≥ 4 mg/day, glibenclamide ≥ 2.5 mg/day, or gliclazide ≥ 40 mg/day) and those on low-dose SU. HbA1c and FBS tended to improve in patients on low-dose SU and the daily insulin dose was also significantly lower in these two groups of patients during the observation period (Fig. 4a-d). No significant changes were seen in body weight in these two groups during the observation period.

DISCUSSION

For treatment of patients with type 2 diabetes who fail to achieve good glycemic control with oral hypoglycemic agents, the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) Consensus Algorithm recommends treatment with a long-acting insulin analog as the next step, in order to normalize fasting blood glucose through basal insulin replacement, leading to better glycemic control [10]. In Japan as well, Goto *et al.* [11] showed that BOT with insulin glargine improved glycemic control in patients with type 2 diabetes who were on high-dose SUs. Apart from this report, however, there are only a few studies on the usefulness of

BOT in Japan. At our institution, 122 patients received BOT during the observation period, making this the largest study of improvement in glycemic control following the introduction of BOT to Japanese patients. In this study, we examined the clinical characteristics of 122 patients, and also 57 subjects in whom follow-up for at least 12 months was possible. The inclusion of the latter group was to examine more closely the therapeutic effect of BOT in Japanese patients with type 2 diabetes after eliminating seasonal variation in glycemic control. The results demonstrated improvement of HbA1c to a mean level of 7% in all patients as well as in the 57 patients who participated in the 12-month long-term study. Although daily insulin doses significantly increased during the observation period, no severe hypoglycemic events were registered during this period. This can be attributed to the sustained action of insulin glargine, which enables a slow increase in insulin level without causing hypoglycemia. Furthermore, good glycemic control was maintained while reducing the oral dosage of SU. As this indicates a smooth transition to insulin-based treatment achieved on an outpatient basis, BOT has the potential to be a very useful protocol in clinical practice. Our result of improved glycemic control are similar to those reported in previous Japanese [11] and overseas studies [7]. However, unlike the overseas reports, we observed no significant weight gain in our patients. This difference can be attributed to racial differences in the etiology of diabetes and the relatively slow increase in insulin dose in our protocol, since any increase in insulin dosage was left to the discretion of the attending physicians. Thorough diabetes education provided

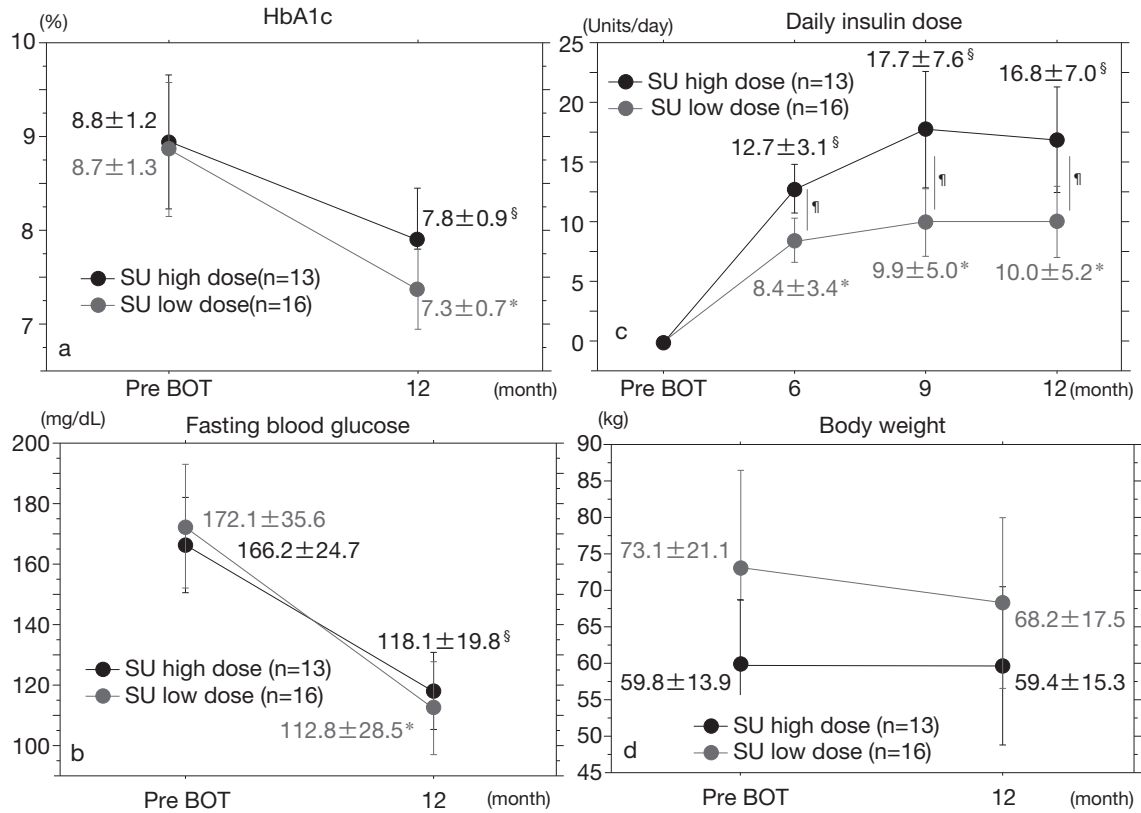


Fig. 4 Comparison of changes in clinical parameters over 12-month period in patients on high-dose and low-dose SU hypoglycemic agents. Data are mean \pm SD. [†] $p < 0.05$ vs high-dose SU group, [§] $p < 0.05$, vs Pre-BOT, ^{*} $p < 0.05$, vs Pre-BOT.

by the healthcare staff may also be a factor, since all our patients received training in blood glucose self-measurement techniques at the time of introduction of insulin therapy. Existing oral hypoglycemic agents are usually continued as part of the BOT. Our study showed that SU dosages were reduced after the introduction of insulin therapy. Since this study was observational in nature, it remains speculative, but this SU dose reduction may have occurred partly because insulin therapy improved glycemic control, thereby eliminating glucose toxicity and resulting in improved insulin secretory capacity and responsiveness to the drugs.

We also evaluated the therapeutic effects of the introduction of BOT according to the class of oral hypoglycemic agents. The results showed no differences between patients on insulin-secreting drugs and those on the non-insulin-secreting drugs with regard to the degree of improvement in fasting blood glucose levels (Fig. 3a). In the non-insulin-secreting drugs, however, HbA1c levels improved significantly, and insulin doses were significantly lower, in comparison with the insulin-secreting drugs (Fig. 3b, 3c). In the previous report, as for the BOT, cases introduced into a high-dose of insulin-secreting drugs were often found. On the other hand, in our report, we introduce BOT for the case of low-dose insulin-secreting drugs or non-insulin-secreting drugs. This is the first report that as concerned about the efficacy of blood glucose improvement by the BOT in the case of low-dose insulin-secreting drugs and non-insulin-secreting drugs. SUs and glinides were the most commonly used oral hypoglycemic agents at

the time of introduction of BOT. We also examined the therapeutic effects of BOT according to the SU dose and the use of glinides. Patients on high-dose SU had significantly higher HbA1c levels after the introduction of BOT, and were on a larger dose of insulin. This could be due to the fact that SUs induce apoptosis of β cells [12], or because β cells become dysfunctional when insulin-secreting drugs such as SU agents, are used for a certain period of time, as suggested by the UK Prospective Diabetes Study (UKPDS) [13]. It has also been suggested that the effect of SU agents becomes dose-independent at much lower doses than with other oral hypoglycemic agents [14]. When glycemic control becomes difficult with SU agents, insulin therapy should be introduced as soon as possible, in other words, while SU dosages are still low.

In conclusion, our results indicate that BOT with insulin glargine is a useful strategy in clinical practice that can achieve good glycemic control without causing serious hypoglycemia. The introduction of BOT allows reduction of SU dose in patients with type 2 diabetes who have failed to achieve good glycemic control with oral hypoglycemic agents alone. The introduction of this therapy before exhaustion of pancreatic β cells may increase its effectiveness.

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The authors declare no competing financial interests.

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