

Efficacy and Safety of Basal-Supported Prandial GLP-1 Receptor Agonist Therapy

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Abstract

Aim: To assess the safety and efficacy of basal-supported prandial GLP-1 receptor agonist therapy (BPT)* in type 2 diabetes mellitus (T2DM). **Methods:** Patients with T2DM, who had previously received insulin injection therapy and who had had their treatment switched to BPT (liraglutide), were retrospectively recruited. The efficacy of BPT was assessed by determining changes in HbA1c, body weight and total daily insulin dose from baseline to 4 months after BPT initiation. Safety was assessed by comparing the frequency of hypoglycemic episodes at baseline and after 4 months. The Wilcoxon test was used to analyze changes in parameters throughout the study period. **Results:** Twenty-nine patients, previously treated with basal-supported oral therapy (BOT), basal-bolus insulin, or pre-mixed insulin, were recruited. When analyzed together, there was no change in HbA1c throughout the study period, but body weight decreased (baseline 68.8 ± 13.2 kg vs. month 4 67.3 ± 13.1 kg; $p < 0.001$). Total daily insulin dose decreased after 4 months (baseline 24.4 ± 15.5 U/day vs. month 4 14.7 ± 9.2 U/day; $p < 0.001$), and there was no change in the frequency of hypoglycemic episodes. Analysis was conducted within sub-groups based on previous treatment modality. In the BOT group, HbA1c decreased from baseline after 2 months and body weight did not change throughout the study period. In both the basal-bolus insulin group and the pre-mixed insulin group, HbA1c remained steady throughout and there was a decrease in body weight. No change in the frequency of hypoglycemia was observed in any of the sub-groups. **Conclusion:** BPT in T2DM was associated with weight loss without changes in glycemic control over 4 months, suggesting that it may be an effective and safe therapy.

Keywords

Basal Insulin, Combination Therapy, GLP-1 Receptor agonists, HbA1c, Type 2 Diabetes Mellitus

1. Introduction

According to the International Diabetes Federation, the prevalence of diabetes is

growing rapidly worldwide. Some 415 million people, or 8.8% of adults aged 20 - 79 years, have diabetes; among these, 94.2 million people (22.7%) are aged 65 - 79 years. If these trends continue, by 2040 some 642 million people, or one adult in 10, will have diabetes [1]. Diabetes is a chronic progressive disease, and as the disease duration increases, endogenous insulin secretion is reduced. In many patients, glycemic control deteriorates despite the use of multiple oral hypoglycemic agents (OHA). In such cases, improvement of glycemic control by insulin injection is required to relieve glucose toxicity [2] [3] [4] [5].

According to a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes [6], when introducing insulin treatment, it is recommended to begin with a basal insulin. If the patient is still unable to achieve adequate glycemic control, basal-plus therapy—which adds an additional insulin to a basal insulin step—or pre-mixed insulin therapy could be considered. If glycemic control is still not adequate, it is recommended to shift to multiple daily injection of insulin.

The combined treatment of a basal insulin and an additional insulin can be effective in the strict management of blood glucose; however, the increased number of injections associated with this may lead to a decline in quality of life [7], and there is a risk of hypoglycemia and increased body weight because of an increase in total daily dose [2]. Hypoglycemia in elderly patients, in particular, is often asymptomatic and can become more severe in many cases. Intensive therapy in the ACCORD trial was associated with a 22% increase in all cause death and a 3-fold increase in severe hypoglycemia [8].

From several recent studies, it is becoming clear that excessive strict blood sugar management leads to cognitive impairment [9] and to increased cardiovascular risk [10]. In May 2016, the joint commission of the Japan Diabetes Society and the Japan Geriatrics Society indicated a new management target value that considered risk of cognitive dysfunction, activities of daily living and severe hypoglycemia in elderly patients with diabetes [11]. As an alternative to basal-supported oral therapy (BOT) and basal-bolus, basal-supported prandial GLP-1 receptor agonist therapy (BPT) may be effective and safe because of a lower risk of hypoglycemia and body weight gain [12]. In this study, we investigated the efficacy and safety of BPT in patients with type 2 diabetes.

2. Materials and Methods

2.1. Subjects

Type 2 diabetic patients who had been treated with BOT, pre-mixed insulin, or basal-bolus participated in the current study, and their treatment was changed to BPT. We investigated the efficacy and safety of BPT compared with patients' previous therapeutic method.

2.2. Study Design

We retrospectively enrolled patients with type 2 diabetes who had originally received insulin injection therapy and had subsequently changed to BPT (using li-

raglutide) in Kitasato Institute Hospital, Tokyo, Japan, between September 2014 and April 2016. Inclusion criteria were patients with type 2 diabetes treated with insulin in addition to diet and exercise therapy. We excluded patients who used exenatide or lixisenatide because they were rare in Kitasato Institute Hospital and because these GLP-1 receptor agonists have a different time action to liraglutide.

To assess efficacy, we measured changes in HbA1c, body weight and total daily insulin dose. To assess safety, we determined the frequency of hypoglycemia, which was calculated as times of [hypoglycemia/times of Self-Monitoring of Blood Glucose] \times 100.

All protocols for this research project were approved by the institutional review board of Kitasato Institute Hospital, and conform to the provisions of the Declaration of Helsinki in 1995. Informed consent was obtained from study participants in the form of an opt-out option (approved by the ethical review board at our hospital), and their anonymity was preserved.

2.3. Statistical Analysis

We used SPSS software ver.24 for data analysis. The Wilcoxon test was used to analyze comparisons of baseline to 2- and 4-month time points, and the level of significance was set to $p < 0.05$. Data are expressed as mean \pm SD or frequency (%).

3. Results

Twenty-nine patients were enrolled in this study. They had been previously treated with BOT (8), basal-bolus insulin (11) and pre-mixed insulin (10). All subjects were administrated liraglutide with basal insulin when their therapy was shifted to BPT. Baseline data of subjects are shown in **Table 1**. Some subjects were taking OHA; when subjects' treatments were changed to BPT, only DPP-4 inhibitors were discontinued, with other agents continued. Doses of basal insulin were coordinated appropriately by the doctor. Liraglutide was initially administrated at 0.3 mg, with the dose subsequently incremented to 0.9 mg. We performed dose adjustment based on digestive symptoms such as vomiting or loss of appetite. The period of observation was approximately 4 months. We assessed HbA1c (National Glycohemoglobin Standardization Program units) and body weight at 2 and 4 months after changing to BPT, and the frequency of hypoglycemia at 4 months (**Table 2**).

HbA1c in study subjects was $7.9\% \pm 0.9\%$ at baseline, $7.8\% \pm 0.8\%$ at month 2 ($p = 0.238$) and $7.9\% \pm 0.9\%$ at month 4 ($p = 0.983$), representing no change in HbA1c. Body weight was 68.8 ± 13.2 kg at baseline, 67.7 ± 13.2 kg ($p < 0.001$) at month 2 and 67.3 ± 13.1 kg ($p < 0.001$) at month 4, representing a statistically significant decrease from baseline at both time points. The mean of weight change was -1.11 ± 1.36 kg from baseline to month 2, -1.66 ± 2.07 kg from baseline to month 4. Liraglutide dose was 0.82 ± 0.18 mg/day at baseline. There was no significant change in basal insulin dose between baseline ($13.6 \pm$

Table 1. Background of subjects (Mean \pm SD).

	All	BOT	BBT	MIX
Number of patient(person)	29	8	11	10
Age (year old)	64.7 \pm 11.4	63.4 \pm 14.3	63.5 \pm 11.4	67.2 \pm 9.5
Sex(Male:Female)	19:10	5:3	9:2	5:5
Duration(year)	19.9 \pm 9.3	22.6 \pm 9.5	17.7 \pm 7.1	20.3 \pm 13.9
Body weight(kg)	68.8 \pm 13.2	63.8 \pm 8.4	67.8 \pm 12.5	74.0 \pm 16.0
BMI	25.1 \pm 3.9	24.3 \pm 1.6	24.5 \pm 4.3	27.1 \pm 5.0
HbA1c(%)	7.9 \pm 0.9	8.6 \pm 0.6	7.5 \pm 0.7	7.9 \pm 1.1
Total daily dose(U/day)	24.4 \pm 15.5	11.6 \pm 5.7	24.1 \pm 8.6	35.0 \pm 19.2
Dose of basal insulin(U/day)	13.6 \pm 10.2	11.6 \pm 5.7	11.1 \pm 8.5	20.5 \pm 10.7
Dose of prandial insulin(U/day)	9.4 \pm 9.1	0	13.0 \pm 4.7	14.5 \pm 9.9
Number of patient used OHA(person)	25	8	9	8
SU	4	2	1	1
DPP-4 inhibitor	23	8	9	6
Biguanide	10	3	4	3
Thiazolidine	1	0	0	1
α -GI	0	0	0	0
Glinide	0	0	0	0

Table 2. Frequency of hypoglycemia (%) Times of hypoglycemia/Times of Self-Monitoring of Blood Glucose \times 100.

Method	Baseline	4M	P value
All	0.31	0.26	0.779
BOT	0.38	0.18	0.655
MIX	0.11	0.47	0.285
BBT	0.40	0.10	0.285

BOT: Basal Supported Oral Therapy, BBT: Basal Bolus Therapy, MIX: pre-mixed insulin.

10.2U/day) and month 4 (14.7 \pm 9.2U/day; $p = 0.22$). As prandial insulin was discontinued in all cases, total daily insulin dose decreased from 24.4 \pm 15.5U/day at baseline to 14.7 \pm 9.2 U/day at month 4 ($p < 0.001$) (**Figure 1**). Frequency of hypoglycemia was 0.31% at baseline and 0.26% at month 4 ($p = 0.779$). Other adverse events recorded were anorexia in 6 cases (19.3%), nausea in 4 cases (12.9%), stomachache in 1 case (3.2%), constipation in 1 case and heartburn in 2 cases (6.5%).

Analysis of Previous Treatment Groups

In patients whose treatment had changed from BOT to BPT, HbA1c was 8.6% \pm 0.6% at baseline and 8.0% \pm 0.4% ($p = 0.035$) at month 2, representing a decrease from baseline. HbA1c at month 4 was 8.1% \pm 0.74%; while lower than baseline,

this difference did not reach statistical significance ($p = 0.092$). Body weight was 63.8 ± 8.4 kg at baseline, 63.2 ± 8.5 kg at month 2 ($p = 0.063$) and 63.2 ± 8.1 kg ($p = 0.183$) at month 4, representing no change in body weight. The mean of weight change was -0.65 ± 0.76 kg from baseline to month 2, -0.66 ± 1.16 kg from baseline to month 4. There was no change in basal insulin dose between baseline (11.6 ± 5.7 U) and month 4 (12.5 ± 6.7 U; $p = 0.109$) (Figure 2). There

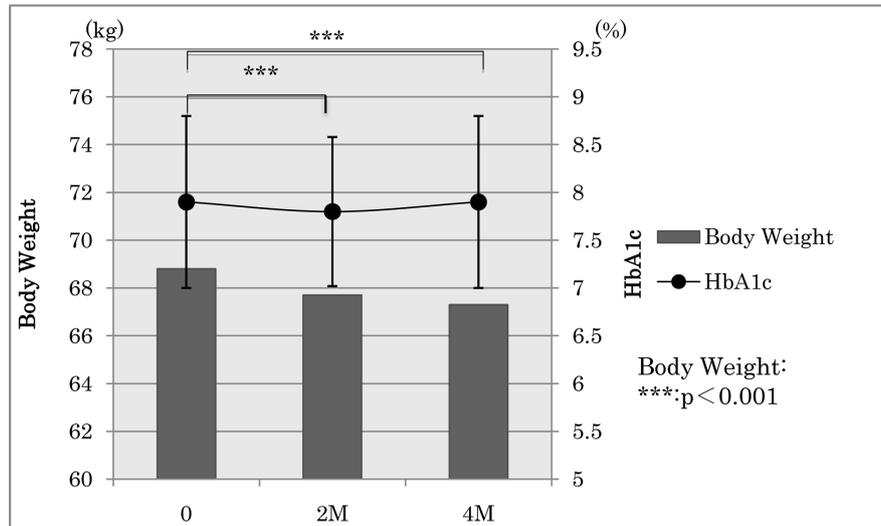


Figure 1. Change in body weight and HbA1c in all subjects. HbA1c in study subjects was $7.9\% \pm 0.9\%$ at baseline, $7.8\% \pm 0.8\%$ at month 2 ($p = 0.238$) and $7.9\% \pm 0.9\%$ at month 4 ($p = 0.983$), representing no change in HbA1c. Body weight was 68.8 ± 13.2 kg at baseline, 67.7 ± 13.2 kg ($p < 0.001$) at month 2 and 67.3 ± 13.1 kg ($p < 0.001$) at month 4, representing a statistically significant decrease from baseline at both time points.

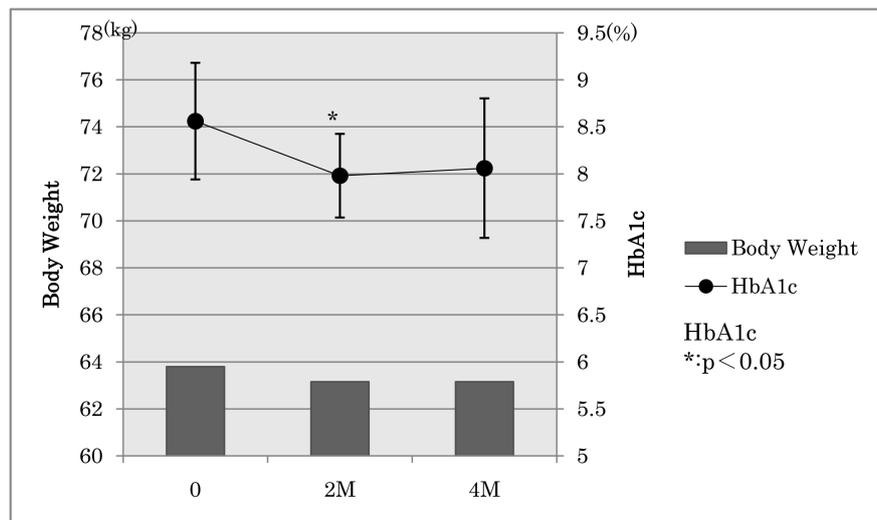


Figure 2. Change in body weight and HbA1c in the BOT group. HbA1c was $8.6\% \pm 0.6\%$ at baseline and $8.0\% \pm 0.4\%$ ($p = 0.035$) at month 2, representing a decrease from baseline. HbA1c at month 4 was $8.1\% \pm 0.74\%$; while lower than baseline, this difference did not reach statistical significance ($p = 0.092$). Body weight was 63.8 ± 8.4 kg at baseline, 63.2 ± 8.5 kg at month 2 ($p = 0.063$) and 63.2 ± 8.1 kg ($p = 0.183$) at month 4, representing no change in body weight.

was no difference in the frequency of hypoglycemia between baseline (0.38%) and month 4 (0.18%; $p = 0.655$).

In patients whose treatment had changed from pre-mixed insulin to BPT, there was no change in HbA1c between baseline ($7.9\% \pm 1.1\%$), month 2 ($8.0\% \pm 1.0\%$; $p = 0.721$) and month 4 ($7.8\% \pm 1.0\%$; $p = 0.959$). Body weight was $74.0\% \pm 16.0$ kg at baseline, 72.3 ± 16.4 kg at month 2 ($p = 0.005$) and 72.4 ± 16.0 kg at month 4 ($p = 0.007$), representing a decrease from baseline (Figure 3). The mean of weight change was -1.53 ± 0.82 kg from baseline to month 2, -1.70 ± 1.18 kg from baseline to month 4. There was no change in basal insulin dose between baseline (20.5 ± 10.7 U) and month 4 (19.4 ± 11.1 U; $p = 0.219$). Total daily dose declined from 35.0 ± 19.2 U at baseline to 19.4 ± 1.1 U at month 4 ($p = 0.005$), in line with discontinuation of prandial insulin. There was no difference between the frequency of hypoglycemia between baseline (0.11%) and month 4 (0.47%; $p = 0.285$).

In patients who had been treated with basal-bolus insulin, HbA1c was $7.5\% \pm 0.7\%$ at baseline, $7.4\% \pm 0.7\%$ at month 2 ($p = 0.721$) and $7.9\% \pm 1.0\%$ at month 4 ($p = 0.142$), representing no statistically significant change. Body weight was 67.9 ± 12.5 kg at baseline and showed a trend towards declining at month 2 (66.9 ± 12.7 kg; $p = 0.142$); this trend reached statistical significance at month 4 (65.6 ± 12.6 kg; $p = 0.021$) (Figure 4). The mean of weight change was -1.07 ± 1.95 kg from baseline to month 2, -2.36 ± 2.91 kg from baseline to month 4. There was no difference between basal insulin dose at baseline (11.1 ± 8.5 U) and month 4 (12.0 ± 7.7 U; $p = 0.285$). Total daily insulin dose declined from 24.1 ± 8.6 U at baseline to 11.9 ± 8.5 U at month 4 ($p = 0.003$), in line with discontinuation of prandial insulin. There was no difference in the frequency of hypoglycemia between baseline (0.4%) and month 4 (0.1%; $p = 0.285$).

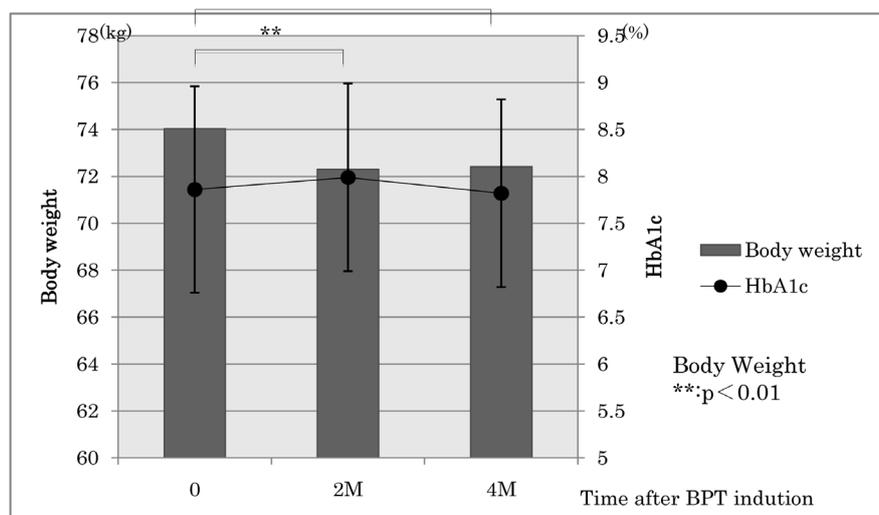


Figure 3. Change in body weight and HbA1c in the pre-mixed insulin group. There was no change in HbA1c between baseline ($7.9\% \pm 1.1\%$), month 2 ($8.0\% \pm 1.0\%$; $p = 0.721$) and month 4 ($7.8\% \pm 1.0\%$; $p = 0.959$). Body weight was 74.0 ± 16.0 kg at baseline, 72.3 ± 16.4 kg at month 2 ($p = 0.005$) and 72.4 ± 16.0 kg at month 4 ($p = 0.007$), representing a decrease from baseline.

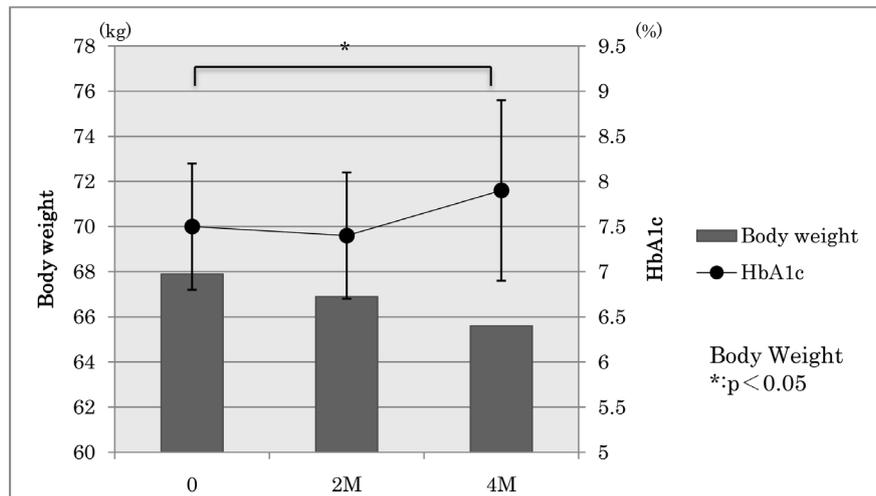


Figure 4. Change in body weight and HbA1c in the basal-bolus insulin group. HbA1c was $7.5 \pm 0.7\%$ at baseline, $7.4 \pm 0.7\%$ at month 2 ($p = 0.721$) and $7.9 \pm 1.0\%$ at month 4 ($p = 0.142$), representing no statistically significant change. Body weight was 67.9 ± 12.5 kg at baseline and showed a trend towards declining at month 2 (66.9 ± 12.7 kg; $p = 0.142$); this trend reached statistical significance at month 4 (65.6 ± 12.6 kg; $p = 0.021$).

4. Discussion

Overall, while no difference was observed in HbA1c over the 4-month study period, a 1.5 kg decrease in body weight was observed ($p < 0.001$). There was no change in the frequency of hypoglycemia. Hypoglycemia and increased body weight are common effects of insulin treatment in diabetes. The fact that patients in this study were able to lose weight without exacerbation of glycemic control and increased hypoglycemia frequency, as well as a reduction in the number of injections, is an advantage of BPT. The appetite-suppressing effect of GLP-1 receptor agonists, as well as a reduction in total daily insulin dose of 9.7U due to discontinuation of prandial insulin, may have contributed to this decrease in body weight.

Among patients who had been treated with different previous therapies, those who had been treated by BOT showed a 0.6% decrease in HbA1c between baseline and month 2 ($p = 0.035$), with no increase in the frequency of hypoglycemia ($p = 0.285$). Though it did not reach significant difference, a trend towards a decrease in body weight (0.6 kg; $p = 0.063$) was observed at month 2. Among those who previously used pre-mixed insulin, although the decrease in HbA1c observed at month 4 was not statistically significant, a 1.7 kg decrease in body weight was observed at month 2 ($p = 0.005$), and this remained statistically significant at month 4 ($p = 0.007$). Though the frequency of hypoglycemia tended to be higher at month 4, this change was not significant. In those who had been previously treated with basal-bolus insulin, a non-statistically significant 0.4% increase in HbA1c was observed. As with the other sub-groups, however, a 2.4 kg decrease in body weight was observed ($p = 0.021$). For obese patients with type 2 diabetes, weight loss without significant exacerbation of glycemic control

could constitute a remarkable advantage of BPT.

As for GLP-1 receptor agonist, although ELIXA study showed lixisenatide had similar rates of major adverse cardiovascular events (MACE) to placebo treatment (HR1.02, 95%CI 0.89 - 1.17) [13], LEADER study showed a 13% reduction in MACE by liraglutide comparing with placebo (95%CI 0.78 - 0.97, $p = 0.01$) [14].

As for combination of GLP-1 receptor agonist and insulin, Ahmann et al. showed addition of GLP-1 receptor agonist to insulin reduced HbA1c significantly [15]. As for comparison of BPT with Basal-Bolus therapy, combination therapy of basal insulin and GLP-1RAs was associated with significant reductions in bodyweight without exacerbation of glycemic control. [16] And according to another analysis, GLP-1 agonist and basal insulin combination offers greater reduction in HbA1c and in body weight with lower risk of hypoglycaemia [17].

Hence, this combination therapy is superior to BOT in glycemic control, and it is superior to Basal-Bolus therapy in weight management. Our study was very small and short-term. Therefore, further studies are needed to assess its longer-term efficacy and safety.

COI Statement

The authors received no financial support for this study. The authors report no conflicts of interest related to this work.

Contribution Statement

Nagahisa T. contributed to data collection, data analysis, discussions, and wrote the manuscript. Tabata M. and Yamada S. contributed to the study concept and design, discussions, and reviewed the manuscript.

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Abbreviation

BOT: Basal Supported Oral Therapy

BBT: Basal Bolus Therapy

MIX: pre-mixed insulin



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