

Original Research Article

Efficacy of thrice-daily biphasic insulin lispro 50/50 in patients with insulin-resistant type 2 diabetes mellitus

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Abstract

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Insulin requirements vary among patients with diabetes due to insulin resistance. For patients whose glycemic goals are not achieved with basal and bolus rapid-acting insulin analog regimens (IBB) owing to insulin resistance, we assigned treatment with basal and thrice-daily biphasic insulin lispro 50/50 (IBB-50). The present study compared the effect of thrice-daily lispro 50/50 combined with insulin glargine in patients with insulin-resistant type 2 diabetes mellitus, was conducted at one medical center. Thirty-eight patients with type 2 diabetes (aged 30–75 years, using stable insulin dose for last 3 months, HbA1c>8.5%) participated in this clinical observational study. The study was continued twelve weeks. Patients who had been treated with stable basal insulin glargine with a prandial bolus rapid-acting insulin analog medication with metformin were switched to basal insulin glargine and thrice-daily biphasic insulin lispro 50/50 and metformin. The patients had a mean age of 56.9 ± 7.0 years, diabetes duration of 15.7 ± 8.3 years, and an HbA1c of $10.7 \pm 1.3\%$. The preprandial rapid-acting insulin analogs were switched to thrice-daily biphasic insulin lispro 50/50. After 12 weeks, fasting and postprandial plasma glucose and HbA1c were significantly reduced. No serious adverse drug reactions, major or nocturnal hypoglycemia were reported. Our study results suggest that the IBB-50 therapy may be necessary to improve glycemic control if patients with type 2 diabetes have high total daily insulin requirements that are inadequately controlled by basal-bolus insulin regimens.

Key words: Biphasic insulin lispro 50, Insulin glargine, Insulin resistance, Type 2 diabetes

INTRODUCTION

Due to progressive metabolic deterioration in patients with type 2 diabetes mellitus (T2DM), the current treatment paradigm is one of gradual regimen intensification. Intensive basal-bolus (IBB) insulin therapy is an “ideal regimen” for physiologic insulin management (Mosenzon, Raz, 2013). When lifestyle modification and basal-bolus treatments fail to achieve adequate glycemic control, an increase of insulin is an appropriate next step, depending on the patient's needs and the physician's practice (Swinen et al., 2009). However, in the United States, only 42% of individuals with T2DM achieved adequate glycemic control, and 1 in 5 patients have poor

glycemic control (i.e., HbA1c $\geq 9.0\%$) (Saaddine et al., 2006).

Several studies have suggested that fasting blood glucose (FBG) and postprandial blood glucose (PPG) are associated with complications of the diabetes (DECODE Study Group., 2001; Cavalot et al., 2011; Lachin et al., 2008; Shiraiwa et al., 2005). Postprandial blood glucose is one of the independent risk factors for macrovascular (DECODE Study Group., 2001; Cavalot et al., 2011) and microvascular complications (Lachin et al., 2008; Shiraiwa et al., 2005) in patients with type 2 diabetes. On the other hand, FBG > 100 mg/dl has been correlated

with increased risk of cardiovascular events (Sarwar et al., 2010). However, mean blood glucose and HbA1c indicate stronger association to diabetes complications than FBG and PPG (Borg et al., 2011).

There is no consensus on how to manage patients who are already using basal and bolus rapid-acting insulin analogs, but require increased insulin doses. However, Miser et al. increased the insulin dose in basal-bolus therapy by 33-40% from baseline, and 36-45% of patients achieved an HbA1c level of $\leq 7.0\%$ (Miser et al., 2010). In another study, in a 24-week, randomized, active-controlled trial, Rosenstock et al. found that 69% of patients in the IBB group achieved an HbA1c value of $< 7.0\%$ (Rosenstock et al., 2008). In this study required an insulin dose increase beyond the pre-study basal dose of 165%.

Although many different types of insulin treatment can try to control hyperglycemia, preprandial insulin therapy with 50/50 premixed insulin would mimic physiological insulin replacement more closely than once-daily basal insulin treatment (Robbins et al., 2007; Kazda et al., 2006). Pre-prandial and PPG levels were lower with thrice-daily premixed insulin lispro 50/50 compared with once-daily insulin glargine (Robbins et al., 2007). Thrice-daily lispro 50/50 treatment resulted in greater improvements in target HbA1c values than thrice daily lispro in combination with sulfonylureas as initial insulin therapy for T2DM (Jacobson et al., 2006). A biphasic insulin lispro 50/50 is expected to have a stronger effect in controlling PPG than other premixed insulin, including less rapid-acting insulin content (Schwartz et al., 2006).

To date, in real practice, there is a lack of scientific reports that investigate optimal approaches to treatment with biphasic insulin lispro 50/50 with basal insulin glargine (IBB-50) and compare the glucose-lowering effectiveness of this regimen in insulin-resistant type 2 diabetes mellitus patients who were already receiving IBB treatment without achieving glycemic control.

To overcome the deficit in insulin with insulin-resistant type 2 diabetes mellitus patients, IBB-50 may be the better option than IBB. Due to the progressive nature of T2DM, a biphasic insulin lispro 50/50 regimen will likely have to be added to basal insulin as an alternative for patients who fail to attain and maintain glycemic targets with IBB treatment alone. The present study focuses on the clinical efficacy and safety profile of prandial IBB-50 in the management of insulin-resistant (total daily insulin requirement, TDIR > 1 U/kg) T2DM compared with the pre-study insulin regime of patients who were receiving basal insulin glargine with a prandial bolus rapid-acting insulin analog and were not achieving glycemic goals.

MATERIAL AND METHODS

Patients were diagnosed with T2DM according to American Diabetes Association criteria. We recruited

patients who had type 2 diabetes and who fulfilled the following criteria: [1] had been treated with stable basal insulin glargine and a prandial bolus rapid-acting insulin analog with metformin for at least 12 weeks; [2] had a total daily insulin requirement of TDIR > 1 U/kg; [3] were 30–75 years of age; [4] had an HbA1c $> 8.5\%$; and [5] had negative screening tests for acromegaly, Cushing's disease, and anti-insulin antibodies.

Patients were excluded if they had any of the following: [1] concomitant chronic disease, including anaemia; [2] chronic kidney disease (individuals with GFR < 60 ml/min/1.73 m²); [3] liver cirrhosis; [4] known cardiovascular disease; [5] a recent acute illness; [6] treatment with other than metformin oral medication during the previous 12 weeks; [7] treatment with steroids; [8] undergoing therapy for a malignancy; [9] suspected or confirmed pregnancy; [10] antilutamic acid decarboxylase antibody-positive; [11] diabetic ketoacidosis in the last 3 months; [12] and evidence of lipodystrophy. All patients provided informed consent and confirmed their willingness to inject insulin and carry out glucose self-monitoring. Before initiation of the study, the details of the study were explained to the patients and written informed consent was obtained from all patients. The approval of the ethics committee of our university was obtained.

Study design, insulin initiation, and titration

The present study, an observational study to compare the effect of thrice-daily lispro 50/50 combined with insulin glargine in patients with insulin-resistant type 2 diabetes mellitus, was conducted at one medical center. The study spanned a 12-week period. Patients visited the clinic every four weeks during the study to determine fasting and post-prandial glucose levels, hypoglycemia, or any adverse effects. Patients who had been treated with stable basal insulin glargine with a prandial bolus rapid-acting insulin analog medication with metformin were switched to IBB-50 and metformin. Patients were allowed to continue metformin, but were prohibited from changing medications during the study. Initial dose was 80% of the total daily insulin dose (IBB); this dose reduction was implemented to lower the likelihood of hypoglycemia. When using IBB-50, 50% of the total daily insulin dose is given as a basal dose (insulin glargine) at 10 am, and 50% as a bolus (biphasic insulin lispro 50/50), divided up before breakfast, lunch, and dinner. We adjusted the doses of both types of insulin (IBB-50) in accordance with changes in patient blood glucose levels.

After the 12-week period, the HbA1c, plasma fasting glucose, and postprandial glucose levels; insulin daily dose; body weight; and the number of hypoglycemic episodes were re-evaluated. Blood glucose measurements were carried out on blood samples collected into tubes containing disodium ethylenediamin-

Table 1. Comparison of anthropometric, clinical and laboratory of the patients with insulin-resistant type 2 diabetes mellitus are demonstrated in IBB and IBB-50 groups (IBB, basal and bolus rapid-acting insulin analog regimens; IBB-50, basal and thrice-daily biphasic insulin lispro 50/50; FBG, fasting blood plasma glucose; PPG, postprandial blood glucose; LDL, low density lipoprotein).

	IBB	IBB-50	p*
Weight (kg)	104.8 ± 20.0	105.8 ± 19.5	0.07
FBG (mg/dl)	279.7 ± 56.5	193.2 ± 60.1	<0.001
PPG (mg/dl)	358.8 ± 61.1	276.7 ± 76.6	<0.001
HbA1c (%)	10.7 ± 1.3	9.6 ± 1.8	0.001
Total insulin dose (units)	123.0 ± 38.0	120.4 ± 33.1	>0.05
Basal insulin dose (units)	52.9 ± 18.7	56.0 ± 17.4	>0.05
Bolus insulin dose (units)	69.7 ± 18.3	64.3 ± 28.2	>0.05
Total cholesterol (median) (mg/dl) ^{&}	201 (102 - 301)	189 (107 - 377)	0.08
Direct LDL cholesterol (median) (mg/dl)	116.1 ± 51.6	110.2 ± 42.4	>0.05
Triglyceride (median) (mg/dl) ^{&}	247 (39 - 628)	233 (75 - 534)	>0.05

[&]: Data expressed as median (min – max)

etetraacetate dihydrate (1.8 mg/ml) and sodium fluoride (1.1 mg/ml). Hematology, biochemistry, physical condition, and vital signs of the patients were also evaluated.

Clinical measurements

Blood samples for assessment of plasma glucose were obtained every four weeks during the study. The patients were provided with blood glucose meters (Contour TS by Bayer). The symptoms of hypoglycemia were taught to the patients, and patients recorded their blood glucose measurement whenever symptoms occurred. If blood glucose was below 70 mg/dl and neuroglycopenic symptoms were not recovered through self-treatment, we accepted it as a major hypoglycemic event.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median, as appropriate. Statistical evaluation of the findings was performed using SPSS 15.0 for Windows statistical software. The descriptive statistics were calculated using frequencies and percentages. Crosstabs and the chi-square test were used to compare categorical parameters. A comparison of amount of insulin doses between before and after study was performed using a paired Student's t-test. To compare the change of HbA1c, FBG, PPG, daily insulin dose, and body weight from baseline, the paired t-test was carried out. The Wilcoxon signed rank test was used for comparison of treatment effects on lipid profile. A p value of < 0.05 was accepted as statistically significant.

RESULTS

A total of 38 patients with T2DM, who showed poor control of blood glucose levels (HbA1c ≥ 8.5%) on their current insulin medication (basal-bolus rapid-acting insulin analog regimens) were enrolled in this study. Their characteristics are shown in Table 1. The amount of insulin used by the subjects on IBB in the pre-study was 123.0 ± 38.0.

The pre-study mean ± SD dose of basal insulin for patients on IBB was 52.9 ± 18.7 units; the rapid-acting bolus insulin analog dose was 23.2 ± 9.4 units in the morning, 23.2 ± 9.4 units in the afternoon, and 23.2 ± 9.4 units in the evening. The corresponding levels after the switch to IBB-50 regimes were 56.0 ± 17.4 for basal insulin and 21.4 ± 6.1 units in the morning, 21.4 ± 6.1 units in the afternoon, and 21.4 ± 6.1 units in the evening for bolus rapid-acting insulin analog.

The amount of insulin used in the IBB-50 group did not differ from that in the pre-study with IBB (Long-acting basal insulin: 52.9 ± 18.7 vs 56.0 ± 17.4; P > 0.05, morning: 23.2 ± 9.4 vs 21.4 ± 6.1, P > 0.05; afternoon: 23.2 ± 9.4 vs 21.4 ± 6.1, P > 0.05; evening: 23.2 ± 9.4 vs 21.4 ± 6.1; P > 0.05, respectively; Figure 1, Table 1).

Compared with levels observed in the pre-study with IBB, IBB-50 significantly suppressed FBG and post-blood glucose elevations, and HbA1c (279.7 ± 56.5 vs 193.2 ± 60.1, P < 0.001; 358.8 ± 61.1 vs 276.7 ± 76.6, P < 0.001; 10.7 ± 1.3 vs 9.6 ± 1.8, P = 0.001, respectively; see Table 1). The comparison of FBG, PPG, and HbA1c levels in IBB vs IBB-50 are presented in Figures 2, 3, and 4, respectively.

Only 11% of patients were able to reach targeted HbA1c values of < 7% on the IBB-50. At week 12, mean changes from baseline FBG values were -86.5 mg/dl for the IBB-50 regimen. At week 12, mean changes from

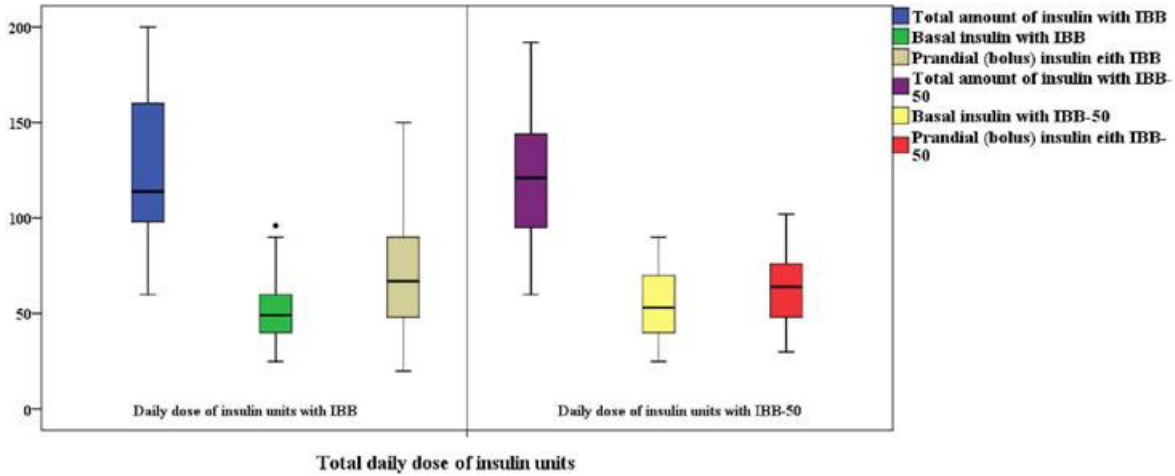


Figure 1. The total daily dose of insulin units used in our study has demonstrated in the IBB and IBB-50 (IBB, basal and bolus rapid-acting insulin analog regimens; IBB-50, basal and thrice-daily biphasic insulin lispro 50/50).

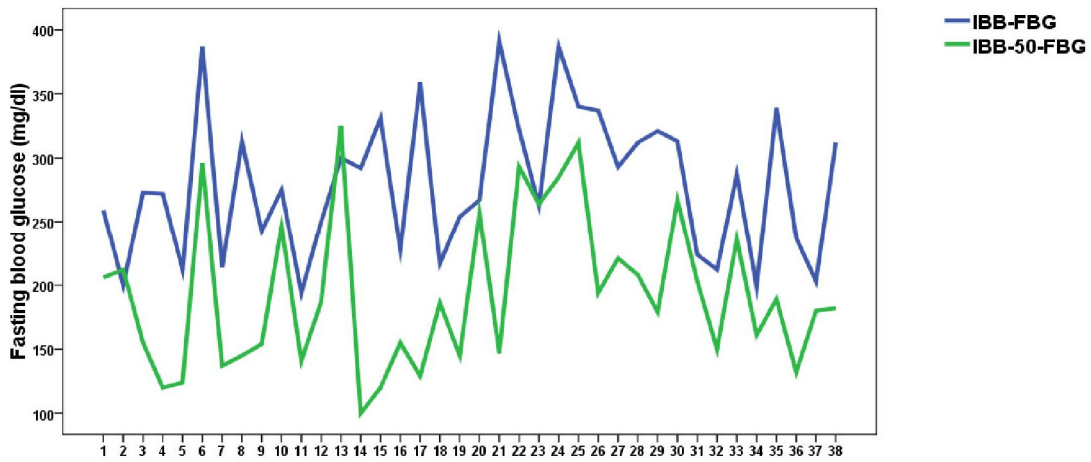


Figure 2. The comparison of FBG levels in IBB vs IBB-50 are demonstrated in patients with insulin-resistant type 2 diabetes mellitus (IBB, basal and bolus rapid-acting insulin analog regimens; IBB-50, basal and thrice-daily biphasic insulin lispro 50/50; FBG, fasting blood glucose).

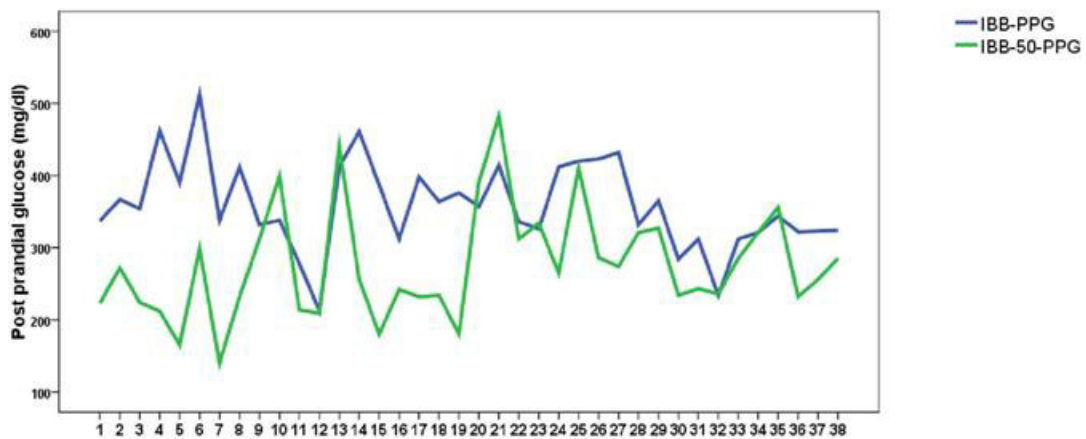


Figure 3. The comparison of PPG levels in IBB vs IBB-50 are demonstrated in patients with insulin-resistant type 2 diabetes mellitus (IBB, basal and bolus rapid-acting insulin analog regimens; IBB-50, basal and thrice-daily biphasic insulin lispro 50/50; PPG, postprandial blood glucose).

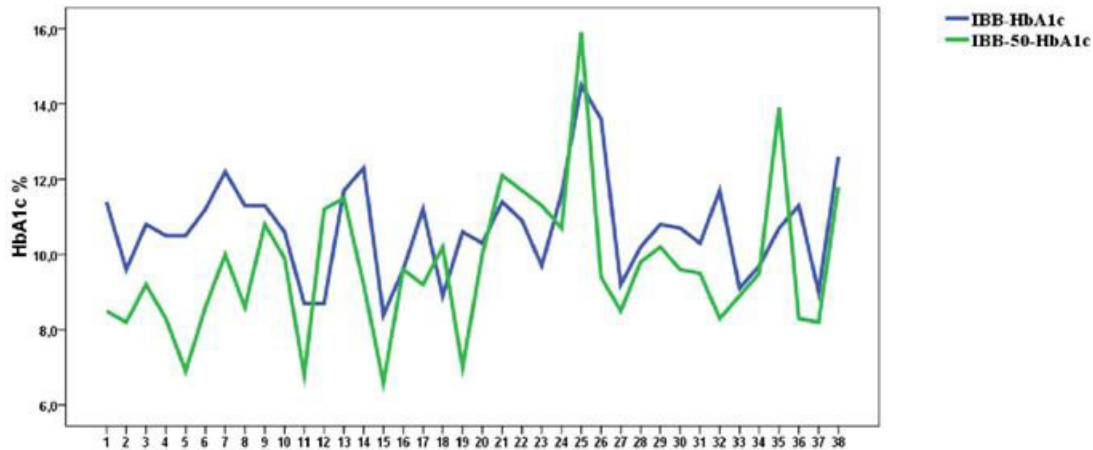


Figure 4. The comparison of HbA1c levels in IBB vs IBB-50 are demonstrated in patients with insulin-resistant type 2 diabetes mellitus (IBB, basal and bolus rapid-acting insulin analog regimens; IBB-50, basal and thrice-daily biphasic insulin lispro 50/50).

baseline PPG values were -82 mg/dl for the IBB-50 regimen. Finally, mean changes from baseline HbA1c values were -1.0% for the IBB-50 regimen.

No severe hypoglycemic symptoms were observed in any of the patients and IBB was safely substituted by IBB-50. No significant differences were found between IBB and IBB-50 for lipid profile (Table 1). Between the baseline and 12 weeks, body weight increased by approximately 1 kg (Table 1). The laboratory results for blood chemistry at the end of the IBB-50 trial were similar to those at baseline (Table 1).

DISCUSSION

There is no established recommendation for how insulin treatment should be advanced in patients who do not achieve glycemic control with IBB therapy. We report here the results of a 12-week trial study comparing IBB-50 insulin treatment in patients with T2DM who failed therapy with administered IBB. The mean baseline HbA1c level was 10.7% in the pre-study with IBB. Clearly, the HbA1c levels for this cohort at baseline indicated poorly controlled T2DM at baseline. In this cohort, patients who switched from pre-study IBB to an IBB-50 regimen experienced significant improvement in HbA1c, FBG, and PPG values. Notably, no major dose titration was required to improve glycemic control for this 12-week evaluation period of IBB-50. Glycemic control appeared to improve with IBB-50. The effectiveness of treatment was associated with no nocturnal or major hypoglycemia events reported during treatment with IBB-50. Improvement of glycemic control with intensive insulin therapy causes weight gain, a frequently undesired result. In the analysis, body weight did not significantly increase in patients on IBB-50.

Morning fasting glucose control was not optimal with

evening mealtime injections of thrice-daily biphasic insulin lispro 50/50 in the recent (Rosenstock et al., 2008) study, as indicated by the daily insulin pharmacodynamics profiles. In this study, the lispro mix 50/50 was changed to lispro mix 75/25 before evening if the FBG was higher than 110 mg/dl (Rosenstock et al., 2008). In previous studies (Robbins et al., 2007; Kazda et al., 2006), FBG levels were significantly lower in patients treated with once-daily insulin glargine compared with those treated with thrice-daily insulin lispro 50/50. Controlling the evening dose of insulin lispro 50/50 was difficult because nocturnal hypoglycemia could be induced if the evening insulin dose of lispro 50/50 were increased to reduce morning fasting glucose levels adequately. Monnier et al. (Monnier et al., 2003) reported that the relative contribution of FBG to overall glycemic levels was 70% in patients with an HbA1c value of 10.2% and decreased as HbA1c levels decreased. Thus, we used insulin glargine with biphasic insulin lispro 50/50 adjusted to focus on lowering fasting glucose levels and pre-prandial glucose when the HbA1c value approaches 10.7%. In our study, higher doses of the neutral protamine lispro part of insulin 50% with insulin glargine provided better morning fasting glucose and pre-prandial glucose levels.

Our strategy was based on prandial premixed therapy utilizing insulin lispro 50/50 three times daily with insulin glargine in patients with insulin-resistant type 2 diabetes mellitus. In clinical practice, use of insulin lispro 50/50 three times daily is based on the possibility of lowering both the FBG and PPG frequently encountered in patients with advanced T2DM (Rosenstock et al., 2008).

The use of a premixed insulin formulation containing a higher proportion of basal insulin may have been an important factor in lowering FBG in our study. For this reason, thrice-daily biphasic insulin lispro 50/50 injection is expected to allow adequate reduction of postprandial

blood glucose levels and sufficient reduction of preprandial blood glucose levels. It is possible that the basal parts of thrice-daily biphasic insulin lispro 50/50 contributed not only to assisting basal insulin but also to extinction of insulin resistance. In this study, unique premixed insulin formulations consisting of 50% insulin lispro and 50% insulin lispro protamine suspension administered before each meal provided an effective alternative approach to optimizing basal insulin therapy in patients using a preprandial rapid-acting insulin analog. We adjusted the doses (no major changes) of both types of insulin (IBB-50) in accordance with changes in the blood glucose levels of the patients.

There is increasing evidence that postprandial blood glucose excursion has a harmful effect on the arterial wall and is involved in both macrovascular (DECODE Study Group, 2001; Cavalot et al., 2011) and microvascular (Lachin et al., 2008; Shiraiwa et al., 2005) complications of diabetes. Strategies to decrease postprandial blood glucose concentrations are essential to reduce complications in patients with type 2 diabetes. Plasma glucose level peaks generally do not exceed 140 mg/dl sixty minutes after the start of a meal, and revert to preprandial levels after about three hours in healthy individuals. However, in T2DM, because of the abnormalities in insulin and glucagon secretion, peripheral glucose utilities, and increased hepatic glucose production, PPG levels are higher than normal (ADA, 2001). Because the absorption of food persists for 5-6 h after a meal, this results in sustained hyperglycemia in individuals with type 2 diabetes, which may be associated with increased oxidative stress, impaired endothelial function, and other deleterious effects on the vascular system. On the other hand, prolonged or large meals may produce a slightly delayed spike in blood glucose.

Effective treatment for post-prandial hyperglycemia is a primary target for treatment to reduce the long-term risks and complications of hyperglycemia. This failure of IBB therapy might be explained by a lack of appropriate prandial insulin coverage after lunch or inappropriate postprandial glycemic control after breakfast and dinner in patients with insulin-resistant type 2 diabetes mellitus. Biphasic insulin lispro 50/50 preparation is expected to have a more potent effect in suppressing postprandial hyperglycemia than the rapid-acting insulin analog¹⁵, especially with insulin-resistant type 2 diabetes mellitus. At the end of the study, the amount of insulin used in the IBB-50 group did not differ from the pre-study levels of IBB (123.0 ± 38.0 vs 120.4 ± 33.1 ; and 1.16 and 1.15 U/kg, respectively). Further, IBB-50 was used with metformin in our study, as combining insulin therapy with this oral antihyperglycemic medication can decrease insulin resistance and insulin requirements and can prevent the weight gain associated with insulin treatment (Douek et al., 2005).

Study Limitations

Most patients (> 85%) in this sub-study did not achieve an HbA1c value < 7.0%. Titration of insulin doses could not be intensive enough for several reasons. The lack of a specific algorithm for insulin adjustments to IBB-50 likely resulted in suboptimal glycemic control; this implies that the need for directive guidance to overcome “clinical inertia” should be explored further. A goal of diabetes treatment is to achieve glycemic targets with minimal hypoglycemia, longer duration of diabetes mellitus and particularly severe hypoglycemia and noncompliance with recommended regimens. The study was of relatively short duration and the data is from a single center, which may not represent the population. These findings indicate that the recommended HbA1c targets could have been achieved at finalization of the present trial if a longer trial and a more aggressive titration regimen had been applied.

CONCLUSIONS

For patients with T2DM who cannot achieve adequate glycemic control with IBB plus metformin, switching to the proposed treatment with IBB-50 yielded better glycemic control in patients with insulin-resistant type 2 diabetes mellitus.

Conflict of Interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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