Efficacy of Long-acting Insulin Analog Insulin Glargine at High Dosage for Basal-bolus Insulin Therapy in Patients with Type 2 Diabetes

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Objective: Attempts to achieve strict glycemic control with basal-bolus insulin therapy required increased dosages of neutral protamine Hagedorn (NPH) insulin. However, high dosage of NPH insulin often occurs nocturnal hypoglycemia. Insulin glargine can simulate normal basal insulin secretion with its flat time-action profiles. To confirm the efficacy of insulin glargine we investigated the type2 diabetic patients on basal-bolus insulin therapy whose basal insulin was switched from NPH insulin to insulin glargine.

Methods: The Japanese 400 patients with type 2 diabetes on basal-bolus insulin therapy whose basal insulin was switched from NPH insulin to insulin glargine were followed-up. After the switching, the basal insulin was increased with reference to the self-monitoring of blood glucose results, with the aim of maintaining fasting blood sugar (FBS) level at 110 mg/dL, and simultaneously reducing the bolus insulin dosage to maintain the total daily insulin dosage.

Results: We were able to lower FBS significantly with almost no serious hypoglycemia. HbA_{1c} also improved significantly. The improvements in FBS and HbA_{1c} levels did not require a significant increase in the total insulin dosage.

Conclusion: Our results suggest that basal insulin supplementation using insulin glargine is a useful method to control not only FBS but also HbA_{1c}.

Key words: Glargine, Insulin, Type 2 Diabetes Mellitus

INTRODUCTION

The results of the United Kingdom Prospective Diabetes Study (UKPDS) and the Kumamoto Study have clearly indicated that strict glycemic control using intensive insulin therapy significantly reduces the frequency of diabetic complications, confirming the usefulness of intensive insulin therapy in type 2 diabetic patients [1, 2]. Furthermore, the increased adoption of self-monitoring of blood glucose (SMBG) and innovations in insulin injection devices has led to widespread use of intensive insulin therapy (basal-bolus insulin therapy).

The use of rapidly acting insulin analogs allows rapid reduction in blood sugar levels (BSLs) not achievable with regular insulin. Compared with standard insulin, the new long-acting insulin analogs allow a closer replication of the normal basal insulin secretion profile. The new long-acting insulin analogs, which were designed as replacement for the neutral protamine Hagedorn (NPH) insulin, can increase the aggressive basal-bolus regimen options. Using these compounds, it is easier to achieve strict glycemic control suited to the individual patient's life style. In comparison, attempts to achieve strict glycemic control with basal-bolus regimens required increased dosages of NPH. However, since the peak hypoglycemic effect of NPH insulin occurs 4–6 hours after injection, the negative effects such as nocturnal hypoglycemia, hampered efforts to increase the dosage of NPH insulin at least in some patients. On the other hand, glargine, a long-acting insulin analog insulin, dissolves gradually and is absorbed slowly, thus shows no definite peak in its pharmacokinetic profile [3], allowing the dosage to be increased while avoiding nocturnal hypoglycemia. Although the number of subjects was small, an excellent recent study demonstrated that Japanese type 2 diabetic patients whose basal insulin was switched from NPH insulin to insulin glargine, and the basal insulin dosage was increased while the bolus insulin dosage was decreased with the aim of maintaining fasting blood sugar (FBS) levels below 140 mg/dL achieved better glycemic control [4]. The results of the study showed that the basal/bolus ratio neared 50%, and glycemic control improved with fewer hypoglycemic events [4]. For Japanese patients with type 2 diabetes, the Japan Diabetes Society guidelines for FBS control define FBS between 80 and 110 mg/dL as "excellent" control. However, when we aim for an FBS < 110 mg/dL using NPH insulin, we often experience nocturnal hypoglycemia. In this regard, Riddle *et al.* reported that increasing the dosage of NPH insulin or insulin glargine in type 2 diabetic patients at bedtime, with the aim of maintaining FBS < 100 mg/dL, the

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final FBS and HbA_{1c} levels were similar for both forms of insulin, though the incidence of hypoglycemia was significantly higher in the NPH group [5]. The results of the above study suggest that any increase in the bedtime dose of NPH insulin to achieve the Japan Diabetes Society recommended target of FBS < 110 mg/dL, to achieve the target would be limited due to the potential development of NPH-related hypoglycemia. For safety, this suggests the need for a clinical trial to test the use of NPH insulin at a dose that can achieve FBS levels < 110 mg/dL.

In the present study, type 2 diabetic patients on basal-bolus therapy were switched from NPH insulin to insulin glargine, with the aim of achieving a FBS level of < 110 mg/dL. The clinical course and efficacy of this therapy was monitored closely throughout the study.

MATERIALS AND METHODS

Subjects

The subjects of this study were 400 patients with type 2 diabetes on basal-bolus insulin therapy whose basal insulin was switched from NPH insulin to insulin glargine between October 2007 and September 2009. Inclusion criteria was as follows, patients with type 2 diabetes, on basal-bolus insulin therapy with once or twice daily NPH insulin and regular or rapidly acting bolus insulin for more than three months, age 20–80 years. Patients who had severe or significant hepatic or renal impairment, pregnancy or malignancy, infection were excluded. Patients undergoing this study were informed about the purpose of the study and asked for the consent to use their data in the examination. They were followed-up for at least 12 months. The selected dosage of insulin glargine was equivalent or higher (capped at no more than 20%) than that of NPH insulin. The regular or rapidly acting bolus insulin was also continued at a dosage either equivalent or lower (capped at not less than 20%) than that of the last bolus insulin dosage. After the switching, the basal insulin was increased with reference to the SMBG results, with the aim of maintaining FBS level at 110 mg/dL, and simultaneously reducing the bolus insulin dosage to maintain the total daily insulin dosage as constant as possible. The attending physician changed both the insulin dosages and the timing of changes at routine outpatient appointments.

FBS, HbA_{1c}, daily insulin dosage, basal/bolus ratio, body weight, and body mass index (BMI) were surveyed at 3 months intervals. The final assessment was conducted 12 months after the switching with the aim of eliminating any seasonal influence in BSLs. FBS levels were obtained from the medical and SMBG records [6, 7]. HbA_{1c} levels were measured using high performance liquid chromatography (HPLC), standardized in accordance with the report by the Japan Diabetes Society Committee on the Standardization of Diabetes-Related Laboratory Testing (JDS HbA_{1c}). Then HbA_{1c} is estimated as National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%, according to the recommendations of the Japan Diabetes Society [8]. We also surveyed the incidence of hypoglycemic events requiring hospitalization.

Hypoglycemia was defined symptomatically and by a blood glucose level < 60 mg/dL. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patients required assistance of another person and either accompanied by a blood glucose level < 40 mg/dL or had prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Statistical analysis

Data are expressed as mean ± SD. Differences between groups were examined for statistical significance using the Mann-Whitney U test and the Wilcoxon signed-rank test. A P value of < 0.05 was considered statistically significant. StatView® 4.0 was used to analyze data.

RESULTS

Table 1 lists the anthropometric data of the participating patients. Over the 12 months observation period, the FBS improved significantly from 163.1 ± 50.4 mg/dL to 121.3 ± 37.9 mg/dL ($P < 0.05$, Fig. 1). HbA_{1c} also improved significantly from 8.0 ± 1.4% to 7.6 ± 1.2% ($P < 0.05$, Fig. 1). The final basal/bolus ratio was 47.8 ± 15.1% (Fig. 2). The initial daily insulin dosage was 40.8 ± 23.0 U/day and remained unchanged at the final check (40.3 ± 22.8 U/day, Fig. 2), indicating that the improvements in FBS and HbA_{1c} levels did not require a significant increase in the total insulin dosage. Although no significant increase in body weight was noted after 3 months, body weight increased significantly at 12 months (baseline: 67.1 ± 15.2 kg, 12 months: 68.0 ± 15.7 kg, Fig. 3). BMI also increased significantly as same as body weight (Fig. 3). During the observation period, only one subject experienced severe hypoglycemia requiring hospitalization.

A significant overall increase in body weight was seen in this study, so we attempted to determine the cause by stratifying subjects into the body weight gain subgroups, comprising subjects with ≥ 3 kg body weight gain over 12 months, and body weight loss subgroup, comprising subjects with ≥ 3 kg body weight loss over the 12-month period. Comparison of the clinical background at the time of switching and 12 months later showed no significant differences between subgroups in pre-switching values of FBS, HbA_{1c}, basal/bolus ratios, daily insulin dosages, or body weight. After 12 months, however, HbA_{1c} levels were significantly higher in the body weight gain subgroup at 7.8 ± 1.2% than in the body weight loss subgroup at 7.5 ± 1.6%. However, there were no significant differences between the two subgroups in the basal/bolus ratios, daily insulin dosages, and other clinical parameters (Table 2).

DISCUSSION

When NPH insulin is administered at bedtime, nocturnal hypoglycemia often occurs around 6 hours after administration. Not only does loss of the glucose-lowering effect lead to early morning hyperglycemia, even with bedtime administration, but also the insulin absorption pharmacokinetics can be quite variable following subcutaneous injection [9]. Insulin glargine is in a solution at around pH 4.0, but in the subcutane-

Table 1 Clinical backgrounds

Backgrounds	
Patients number	400
Age (years)	65.6 ± 15.2
Height (cm)	164.9 ± 8.7
Body weight (kg)	67.1 ± 15.2
Body Mass Index (BMI)	24.6 ± 3.2
Gender (male/female)	229/171

Mean ± SD

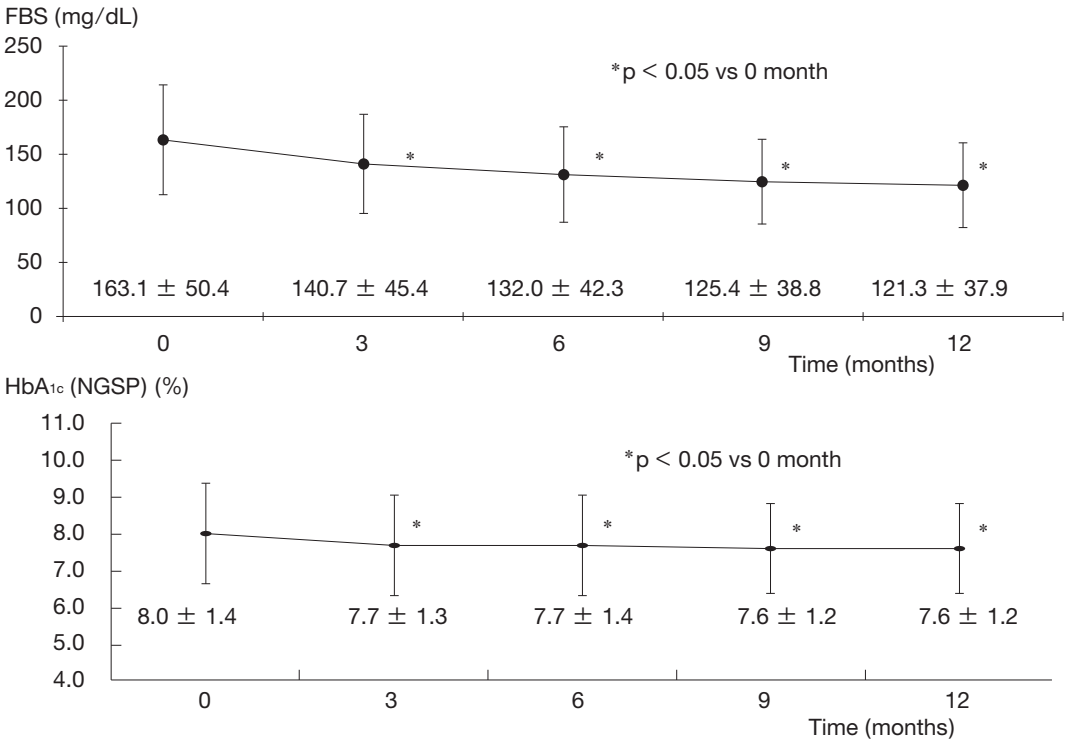

Fig. 1 Serial changes in fasting blood sugar (FBS) and HbA_{1c} (NGSP HbA_{1c})throughout the study period.

ous tissue at around pH 7.4 it undergoes isoelectric precipitation and becomes insoluble. This delays its absorption, yielding a constant glucose-lowering effect over 24 hours with no definite peak in its plasma concentration [3]. The main reason for the elevated early morning FBS seen in type 2 diabetic patients is failure of suppression of hepatic gluconeogenesis overnight, attributed to hepatic insulin resistance and relative lack of insulin. Accordingly, achievement of FBS level of 110 mg/dL, as recommended by the Japan Diabetes Society, requires safe supplementation of insulin in sufficient quantities. Basal insulin supplementation using insulin glargine is therefore a useful method to control early morning FBS. In the present study, by increasing the dosage of insulin glargine to a sufficient dosage, we were able to lower FBS to around 120 mg/dL with almost no serious hypoglycemia.

It is noteworthy that HbA_{1c} levels improved in this study by approximately 0.4%, despite the lack of significant change in the total daily insulin dosage. Naturally, reduction in FBS played a large part in this improvement. It is also possible that improved BSLs before each meal led to improvement of postprandial BSLs. In general, supplementing postprandial secretion with bolus insulin is known to normalize the postprandial glycemic response, thereby improving insulin sensitivity and also FBS levels [10, 11]. On the other hand, one study found that improvement of FBS levels plays a large part in normalizing the postprandial glycemic response [12]. In other words, our results suggest that improvements in FBS levels and BSLs before each meal were accompanied by improvements in postprandial BSLs. We cannot make any firm conclusions because we did not actually measure postprandial BSLs in the present study, but we await with interest the results of further studies. One reason we were able to safely achieve good glycemic control as evidenced by the observed improvement in HbA_{1c}, with only one case of severe hypoglycemia requiring hospitalization, was likely the treatment regimen used in this study. Unlike previous methods that normalized the postprandial glycemic response by increasing the bolus insulin dosage, we lowered BSLs throughout the day by appropriate increases in the basal insulin dosage. When a large proportion of the daily insulin dosage is bolus insulin, the likelihood of sudden hypo-

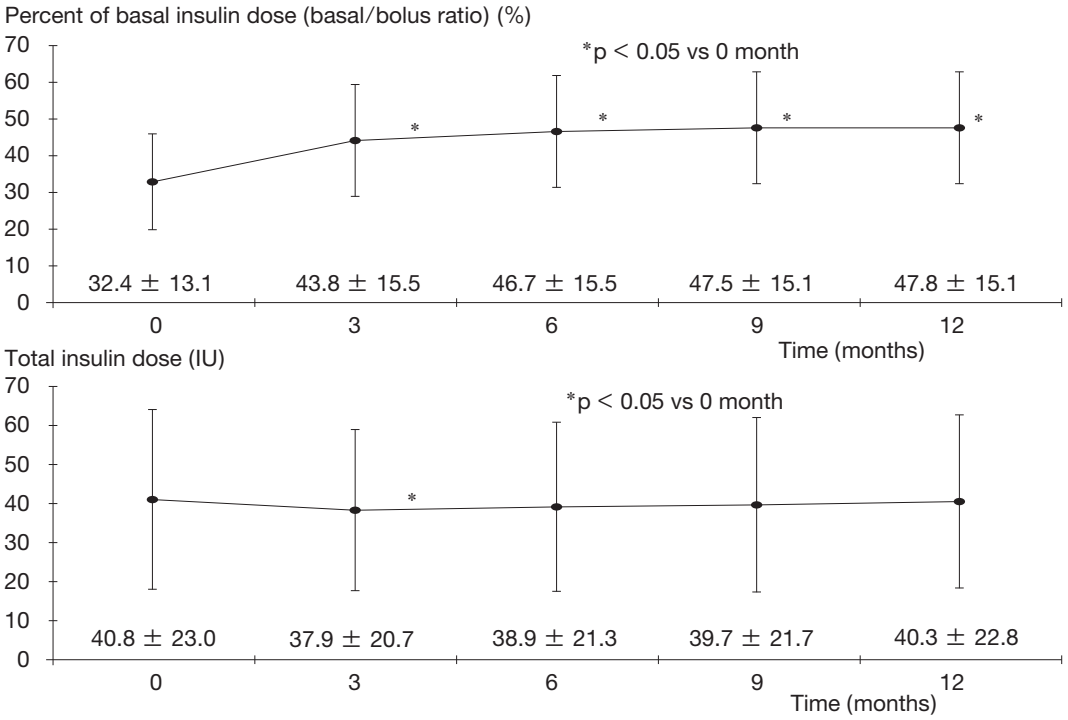

Fig. 2 Serial changes in the percentage of basal insulin dose (basal/bolus ratio) and the total insulin dose throughout the study period.

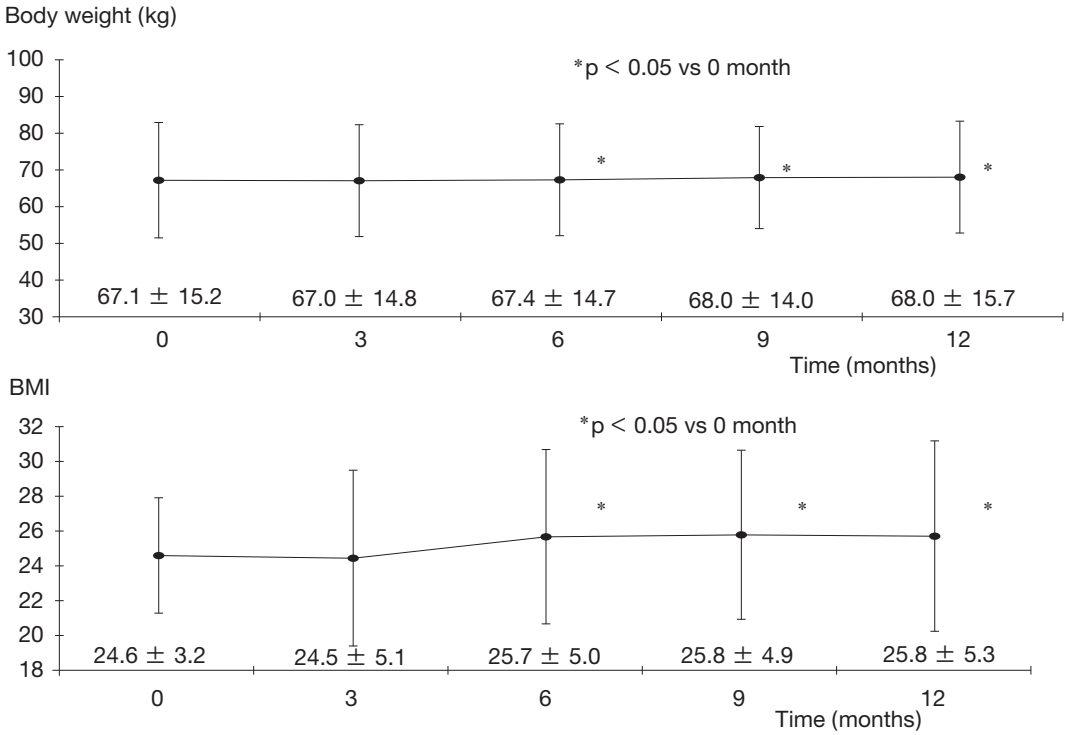

Fig. 3 Serial changes in body weight (BW) and body mass index (BMI) throughout the study period.

glycemic events is high. The latter is related to the fact that the variations of patient's diet, exercise level, and/or the bolus insulin dosage adjustment determined by the patients themselves may be not perfect. In our study, however, we adopted a regimen that included reduction of the dosage of bolus insulin, the cause of sudden change in BSL, and increased the dosage of long-acting basal insulin. This led to not only a sustained mild hypoglycemic effect while fasting, but also reduced variations in BSLs to a minimum due to the reduced proportion of bolus insulin. This suggests that adequate basal insulin supplementation using insulin glargine allows a safer stabilization of BSLs, improvement of short-term glycemic control, and prevention of diabetic complications in the long-term.

With regard to changes in body weight with traditional intensive insulin therapy, the UKPDS Group reported that body weight increases in association with

Table 2 Comparison of clinical backgrounds between body weight gain group and loss group

		Body Weight Gain (n = 66)	Body Weight Loss (n = 32)	p-value
FBS (mg/dL)	0M	165.1 ± 43.6	172.0 ± 54.3	N.S.
	12M	126.3 ± 40.0	123.0 ± 37.0	N.S.
HbA_{1c} (NGSP) (%)	0M	8.2 ± 1.3	8.2 ± 1.7	N.S.
	12M	7.8 ± 1.2	7.5 ± 1.6	p = 0.0349
Basal/Bolus (%)	0M	33.3 ± 12.6	34.0 ± 14.2	N.S.
	12M	49.0 ± 11.7	47.9 ± 17.8	N.S.
Total Inslin (IU)	0M	44.2 ± 24.8	44.5 ± 25.2	N.S.
	12M	47.8 ± 26.8	40.3 ± 21.5	N.S.
Body Weight (kg)	0M	69.7 ± 18.2	70.9 ± 14.5	N.S.
	12M	75.1 ± 18.3	65.4 ± 14.3	N.D.
BMI	0M	25.6 ± 5.5	26.1 ± 4.4	N.S.
	12M	27.6 ± 5.5	24.0 ± 4.2	N.D.

FBS: fasting blood suger, BMI: Body Mass Index, N.S.: not significant, N.D.: not done Mean ± SD

normalization of BSLs. The mechanism of such body weight gain is thought to be due to glucose supplementation, snacking and overeating in association with hypoglycemia induced by the relative overdosage of insulin. The results of this study also showed a significant body weight gain of approximately 1 kg after 12 months. To determine the cause of this body weight gain, we compared subjects with body weight gain (comprising subjects with ≥ 3 kg body weight gain over 12 months) and those with body weight loss (comprising subjects with ≥ 3 kg body weight loss over 12 months). The results showed no significant differences between the two groups in pre-switching clinical parameters, basal/bolus ratios after 12 months, and daily insulin dosages. In contrast, HbA_{1c} levels were significantly higher in the body weight gain group. These results suggest that body weight gain was not associated with the high proportion of basal insulin, but rather by subjects unable to adhere strictly enough to the prescribed diet, who failed to curb their overeating and therefore put on weight. This emphasizes the importance of patient education. Several studies reported significant reductions in the rate of body weight gain with insulin glargine in comparison with NPH insulin [13–15]. We could have perhaps limited the body weight gain observed in this study had we placed more emphasis on diet and exercise, both education and practice, and reinforced the advice concerning body weight at each outpatient appointment. With this in mind, we believe there is a need for a prospective clinical trial, using sufficient basal insulin to achieve FBS levels < 110 mg/dL, at the same time instituting strict diet and exercise regimens.

In this study, we were able to achieve a basal/bolus ratio of about 50%, corresponding to the physiological basal/bolus ratio employed following the introduction of the insulin pump therapy for type 1 diabetes mellitus. In traditional intensive insulin therapy for type 2 diabetes mellitus, NPH insulin usually comprises 25–30% of the total insulin dosage, and Phase 3 clinical trials used insulin glargine at approximately 30% of the total insulin dosage. A recent nationwide survey of Japanese medical institutions found that insulin glargine comprises no more than 35% of the total insulin dosage. The same survey showed that when insulin glargine accounts for 30% of the total insulin dosage, the rates of achieving an HbA_{1c} level of ≤ 7% or ≤ 6.5% are similar to those with NPH insulin, and FBS is maintained at a rather high level of 149 ± 33 mg/dL. This suggests that the benefits of insulin glargine therapy are not being fully expressed. We can assume that a better control could have been achieved in these patients were the advantages of insulin glargine elicited to the fullest extent, safely reducing FBS levels to around the 110 mg/dL mark.

In the present study of 400 subjects, we used insulin glargine at a high basal/bolus ratio with the aim of achieving FBS levels < 110 mg/dL, and confirmed that it is possible to lower both FBS and HbA_{1c} levels safely and without the need to increase the total insulin dosage. Furthermore, we found that the reduction in the bolus insulin dosage was not associated with postprandial hyperglycemia or hyperglycemia before the next meal, as had been our concern, but rather improved postprandial and preprandial BSLs in many patients. Similar results have been reported by other groups [16], with sufficient basal insulin supplementation and normalization of FBS levels, leading to improvement in glycemic response [12], suggesting improved hypoglycemic effect even with reduction in the bolus insulin dosage. To confirm these findings, further prospective multicentre clinical trial is needed, using a sufficient dosage of basal insulin to achieve FBS levels < 110 mg/dL.

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