Replacement of neutral protamine Hagedorn insulin with the long-acting insulin analogue, detemir, improves glycemic control without weight gain in basal–bolus insulin therapy in Japanese patients with type 1 diabetes

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ABSTRACT

Aims/Introduction: The aim of the present study was to evaluate the efficacy of replacing neutral protamine Hagedorn insulin (NPH) with the long-acting insulin analogue, detemir, in clinical practice.

Materials and Methods: We carried out a retrospective study to compare the effects of replacing NPH with detemir in basal–bolus insulin therapy in Japanese patients with type 1 diabetes. A total of 19 patients were enrolled in the study, and changes in hemoglobin A_{1c} (HbA_{1c}), insulin dose, bodyweight, fasting blood glucose levels (FBG), within-patient variability in FBG and prevalence in hypoglycemia were monitored for 12 weeks before replacement and during three periods after replacement; 1–12 weeks (period 1), 13–24 weeks (period 2) and 25–36 weeks (period 3).

Results: HbA_{1c} values improved significantly in periods 2 and 3. Despite the total insulin dose remaining unchanged throughout the study, the basal insulin dose increased from 0.24 to 0.27 IU/kg/day in period 2 and 0.28 IU/kg/day in period 3. Bodyweight decreased from 61.8 to 60.8 kg in period 1, whereas FBG improved throughout the study. Within-patient variability in FBG was lower with detemir treatment than with NPH, despite the number of hypoglycemic episodes increasing significantly after replacement.

Conclusions: These findings show that the weight loss observed in patients was independent of the reduction in calorie intake resulting from less frequent hypoglycemic attacks. In Japanese patients with diabetes who received NPH, replacing NPH with detemir led to improvements in glycemic control without any weight gain. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00066.x, 2010)

KEY WORDS: Insulin detemir, Neutral protamine Hagedorn insulin, Replacement

INTRODUCTION

The importance of intensive glycemic control in reducing the long-term microvascular and macrovascular complications associated with diabetes has been shown in several clinical trials[1–4]. Diabetic patients with deficient insulin secretion are treated routinely with basal–bolus insulin therapy to reproduce endogenous insulin secretion. This therapeutic regimen involves an intermediate or long-acting insulin as the basal insulin and regular or ultra-rapid insulin at each mealtime. The purpose of basal–bolus therapy is to control blood glucose within physiological levels. Recently, long-acting insulin analogues that more accurately reproduce a physiological basal insulin profile have been developed. Detemir is one such long-acting insulin analogue and was released in Japan in December 2007. Its prolonged duration of action is attributable to a combination of increased self-association and albumin binding as a result of acylation of the amino acid in position B29, lysine, by myristic acid[5,6].

In previous clinical trials on Caucasian patients with type 1 or type 2 diabetes, detemir, when compared with neutral protamine Hagedorn insulin (NPH), contributed to improved glycemic control, significantly less within-patient variability in fasting blood glucose levels (FBG) and fewer hypoglycemic episodes[7–15]. Those trials also showed that detemir had an additional benefit in that it resulted in less weight gain compared with NPH[10–16]. Furthermore, Jhee *et al.* reported that the pharmacokinetics of detemir in ascending doses are similar in healthy Japanese and Caucasian subjects[17]. However, the environment, lifestyle and food intake of Japanese subjects are distinct from that of Caucasian subjects, and these differences are one of the important factors to consider in diabetes care. Additionally, recent studies have shown that measurements of hemoglobin A_{1c} (HbA_{1c}) in

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Japanese subjects were significantly lower than in subjects in Europe and the USA[18–20]. Other researchers found that absorption of insulin aspart was higher in Japanese subjects than Caucasian subjects[21]. From these points of view, we cannot apply the results of previous clinical studies to Japanese patients with diabetes.

It is well known that weight gain is often perceived as an inevitable effect of insulin therapy, particularly in patients who strive for tight glycemic control[22,23]. Purnell *et al.* supported the hypothesis that increased weight gain with intensive insulin therapy might be explained, in part, by genetic traits[24]. As the subjects enrolled in many previous studies on detemir had a body mass index (BMI) >26 kg/m[29–16], it remains unclear whether bodyweight decreases in Japanese patients with diabetes with a lower BMI when NPH therapy is replaced by detemir. In contrast, in cases where NPH is replaced by detemir, the initial recommended dose of detemir is approximately 70% of the NPH dose[25]. Furthermore, the reports did not refer to bolus insulin dose and provided limited information in that context. In clinical practice, we encountered some cases that showed a more extreme rise in FBG when the dose of detemir was adjusted to approximately 70% of the NPH dose. There are, however, no published reports on the clinical use of this insulin regimen in Japanese patients with diabetes.

In the present study, we therefore evaluated the effects of replacing NPH with detemir in basal–bolus insulin therapy in 19 Japanese adult patients with type 1 diabetes. Changes in HbA_{1c}, total insulin dose (basal and bolus), bodyweight, FBG, within-patient variability in FBG and hypoglycemic episodes were monitored at 12 weeks before replacement and during the following three periods after replacement; 1–12 weeks (period 1), 13–24 weeks (period 2) and 25–36 weeks (period 3).

MATERIALS AND METHODS

Patients

A total of 59 adult outpatients with diabetes received basal–bolus therapy involving regular or ultra-rapid insulin (bolus insulin) in combination with NPH (basal insulin) at Otsu Municipal Hospital (Otsu, Shiga, Japan), between October 2007 and August 2009. Of these patients, 46 patients (78.0%) had NPH replaced with detemir as the basal insulin. A total of 27 patients were excluded, leaving 19 patients (11 men and 8 women) to be analyzed in the present study. Exclusion criteria included patients with type 2 diabetes, non-compliance, poor glycemic control (HbA_{1c} > 10%), proliferative retinopathy requiring acute treatment, impaired renal or hepatic function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycemia, allergy to insulin, pregnancy, use of systemic glucocorticoids, discontinued treatment with detemir within 36 weeks, switch of the bolus insulin preparations and being treated with premixed insulin before replacement. To analyze the efficacy of replacing NPH with detemir, the clinical course for each patient was divided into four 12-week periods: 12 weeks before administration of detemir (baseline) and 1–12 weeks (period 1), 13–24 weeks (period 2) and 25–36 weeks (period 3) after replacement. In all patients, NPH insulin was replaced with detemir as the basal insulin, with no change in the bolus insulin preparations during the study period. The main reasons for replacement were to improve glycemic control and to reduce variability in FBG. The insulin regimen for each individual was decided by a physician according to the blood glucose profile and lifestyle of the patient. Throughout the study period, the dose of the bolus and basal insulin, and the number of injections of basal insulin were adjusted by a physician according to the blood glucose profiles recorded at each hospital visit. If necessary, the dose of insulin was increased or reduced by 2–4 units to meet target FBG. The dosages of oral antidiabetic drugs remained unchanged throughout the study period. Retinopathy was classified as no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), pre-proliferative diabetic retinopathy (PPDR) or proliferative diabetic retinopathy (PDR). Nephropathy was classified into three stages as normoalbuminuria, microalbuminuria or macroalbuminuria. The present study was carried out in accordance with the Declaration of Helsinki and its amendments. The Ethics Committee of Otsu Municipal Hospital gave its approval for the study.

Insulin Products Administered to the Patients

For bolus insulin injections, the patients received regular insulin (Novorin-R Flex pen; NovoNordisk, Bagsvaerd, Denmark) or ultra-rapid insulin including insulin lispro (Humalog; Eli Lilly, Indianapolis, IN, USA) or insulin aspart (Novo Rapid Flex pen; NovoNordisk). All patients had NPH insulin (Novorin-N Flex pen; NovoNordisk) replaced with long-acting insulin analogue detemir (Revemir Flex pen; NovoNordisk) as the basal insulin.

Biochemical Tests and Monitoring Indexes

HbA_{1c} was measured by a latex agglutination immunoassay using the Determiner HbA_{1c} kit (Kyowa Medex, Tokyo, Japan) and an automatic analyzer (DM-JACK; Kyowa Medex). The inter- and intra-assay coefficients of variation in HbA_{1c} determination ranged from 0.37 to 0.47 and 0.57 to 0.83%, respectively. Self-measured blood glucose (SMBG) was measured by a glucose meter (Glutest Ace; Sanwa Kagaku, Nagoya, Japan). Urinary albumin concentration was determined by a turbidimetric immunoassay (SRL, Tokyo, Japan). Bodyweight was measured at the hospital using a calibrated scale. Basic clinical information on the patients was collected by reviewing medical records and included medical history, clinical progress, laboratory tests, concurrent drugs and time-dependent changes in insulin dose. FBG and incidence of hypoglycemia were collected from the patients' SMBG records. All these data were collected and verified by the patients' physician. Hypoglycemia was defined as a confirmed blood glucose level <70 mg/dL. Hypoglycemia that occurred during sleep from bedtime to getting up in the morning was defined as nocturnal. Severe hypoglycemia was defined by impaired consciousness or convulsions requiring assistance from other persons and the need for an intramuscular injection of

glucagon or intravenous glucose. Using these data, changes in HbA_{1c} values, insulin dose, the percentage of basal insulin dose, bodyweight, FBG, within-patient variability in FBG and frequency of hypoglycemia were analyzed. HbA_{1c} values, insulin dose, the percentage of basal insulin dose and bodyweight were evaluated in all patients, whereas the other values were evaluated in just 16 patients in whom detailed SMBG records were obtained.

Calculations and Statistics

The average values for each parameter were calculated for each 12-week period and the results are expressed as standard error of the mean (SEM) unless otherwise stated. Japan Diabetes Society (JDS), National Glycohemoglobin Standardization Program (NGSP), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values of HbA_{1c} were calculated according to the Consensus and Statement on International Standardization of HbA_{1c} in Japan[26]. Within-patient day-to-day variability in FBG was calculated as the standard deviation of FBG in the morning. The percentage of basal insulin dose was obtained by calculating the ratio of basal insulin dose against total insulin dose. Statistical testing was carried out using paired *t*-tests. This test was used only when each data set had a normal distribution and the same variance. A *P*-value of <0.05 was considered statistically significant. All analyses were carried out using the statistical software Statview ver 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Characteristics

Table 1 shows the clinical characteristics of the subjects at baseline (i.e. 12 weeks before the replacement of NPH with detemir).

Table 1 | Characteristics of the patients at baseline, 12 weeks before replacing neutral protamine Hagedorn insulin with detemir

Parameter	$n = 19$
Male/female (*n*)	11/8
Age (years)	44.5 (10.9)
Duration of diabetes (years)	12.9 (10.0)
Bodyweight (kg)	61.8 (10.0)
Body mass index (kg/m^2)	22.6 (3.4)
JDS HbA_{1c} (%)	7.89 (0.88)
NGSP HbA_{1c} (%)	8.34 (0.90)
IFCC HbA_{1c} (mmol/mol)	65.2 (9.2)
Retinopathy (NDR/SDR/PPDR/PDR), *n*	14/1/2/2
Nephropathy stage (normoalbuminuric/ microalbuminuric/macroalbuminuric), *n*	14/3/2

Each value represents the mean (SD) of the 19 patients in the study. IFCC HbA_{1c}, International Federation of Clinical Chemistry and Laboratory Medicine values; JDS HbA_{1c}, hemoglobin A_{1c} of Japan Diabetes Society values; NDR, no diabetic retinopathy; NGSP HbA_{1c}, hemoglobin A_{1c} of National Glycohemoglobin Standardization Program values; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

Of the 19 patients with type 1 diabetes, 17 patients received basal insulin once a day at bedtime, and two patients received basal insulin twice a day. All the patients had received basal–bolus insulin therapy for 12 months before administration of detemir. No patient was prescribed additional oral antidiabetic drugs during the study.

HbA_{1c} and Bodyweight after Replacement of NPH with Detemir

Table 2 shows the changes in mean values of HbA_{1c} and bodyweight at baseline and during periods 1, 2 and 3 after replacing NPH with detemir. Significant improvements ($P < 0.01$) in HbA_{1c} levels were found during periods 2 and 3 as compared with the baseline. There was a significant weight loss ($P < 0.05$) during period 1 as compared with the baseline. Similarly, there was a trend toward a decrease in bodyweight during period 2 as compared with the baseline, whereas bodyweight tended to regain during period 3.

FBG and Variability in FBG after Replacement of NPH with Detemir

Table 3 shows the changes in mean values of FBG and the day-to-day within-patient variability in FBG at baseline and during the three periods after replacement. There was a significant improvement ($P < 0.05$) in FBG during period 3 as compared with the baseline. In addition, the day-to-day within-patient variability in FBG decreased after administration of detemir. There was a significant reduction ($P < 0.05$) in the value of variation in FBG within-patients during period 1 in comparison with the baseline.

Results of Insulin Dose Adjustment

Changes in mean insulin dose at baseline and in the three periods after replacement are listed in Table 4. The mean dose of basal insulin was significantly increased during period 2 ($P < 0.05$) and period 3 ($P < 0.01$) as compared with the

Table 2 | Changes in mean HbA_{1c} and bodyweight at baseline and in periods 1, 2 and 3 after replacing neutral protamine Hagedorn insulin with detemir

	Baseline	Period 1	Period 2	Period 3
		1–12 weeks	13–24 weeks	25–36 weeks
JDS HbA_{1c} (%)	7.89 (0.20)	7.76 (0.21)	7.44 (0.19)†	7.35 (0.23)†
NGSP HbA_{1c} (%)	8.34 (0.21)	8.21 (0.21)	7.88 (0.19)†	7.79 (0.23)†
IFCC HbA_{1c} (mmol/mol)	65.2 (2.1)	63.8 (2.1)	60.5 (2.0)†	59.6 (2.4)†
Bodyweight (kg)	61.8 (2.3)	60.8 (2.1)*	60.8 (2.2)	61.1 (2.5)

Each value represents the mean (SEM) of the 19 patients in the study. *$P < 0.05$, †$P < 0.01$ *vs* baseline (paired *t*-test).
IFCC HbA_{1c}, International Federation of Clinical Chemistry and Laboratory Medicine values; JDS HbA_{1c}, hemoglobin A_{1c} of Japan Diabetes Society values; NGSP HbA_{1c}, hemoglobin A_{1c} of National Glycohemoglobin Standardization Program values.

Table 3 | Changes in mean fasting blood glucose levels and variability in fasting blood glucose levels at baseline and in periods 1, 2 and 3 after replacing neutral protamine Hagedorn insulin with detemir

	Baseline	Period 1	Period 2	Period 3
		1–12 weeks	13–24 weeks	25–36 weeks
FBG (mg/dL)	166.7 (12.9)	147.2 (5.8)	154.3 (14.7)	140.4 (10.3)*
Variability in FBG (mg/dL)	66.0	57.5*	58.1	57.4

Fasting blood glucose levels (FBG) represents the mean (SEM) of the 16 patients in the study. Variability in FBG represents the mean of the 16 patients in the study. Variability in FBG was calculated as the standard deviation of FBG. *$P < 0.05$ *vs* baseline (paired *t*-test).

baseline. In contrast, the mean dose of bolus insulin was significantly decreased ($P < 0.05$) during period 3. The mean dose of total insulin was unchanged throughout the study period (approximately 0.75 IU/kg/day). The ratio of basal insulin dose to total insulin dose was significantly increased during period 2 ($P < 0.05$) and period 3 ($P < 0.01$) as compared with the baseline.

Frequency of Hypoglycemia after Replacement NPH with Detemir

Table 5 shows the mean frequency of hypoglycemic episodes at baseline and during the three periods after replacing NPH with detemir. Significant increases in the mean frequency of overall hypoglycemia during period 1 ($P < 0.05$) and period 2 ($P < 0.01$) were found as compared with that of the baseline. Similarly, the mean frequency of daytime hypoglycemia increased significantly during period 1 and period 2 (both $P < 0.05$) as compared with that of the baseline. In contrast, the mean frequency of nocturnal hypoglycemia was unchanged throughout the study period. Nocturnal hypoglycemia was confirmed in two cases treated with NPH, but disappeared in one case after replacement of NPH with detemir. No severe hypoglycemic episodes that required external help were found during detemir treatment. Furthermore, no other adverse events were caused by the use of detemir during the study period.

Table 5 | Changes in the mean frequency of hypoglycemia at baseline and in periods 1, 2 and 3 after replacing neutral protamine Hagedorn insulin with detemir

Hypoglycemia (episodes/patient/12 weeks)	Baseline	Period 1	Period 2	Period 3
		1–12 weeks	13–24 weeks	25–36 weeks
Overall	22.1 (6.0)	29.8 (6.6)*	34.4 (8.1)†	30.2 (5.7)
Daytime	21.5 (6.0)	29.4 (6.6)*	33.7 (8.2)*	30.1 (5.7)
Nocturnal	0.6 (0.4)	0.3 (0.3)	0.7 (0.7)	0.1 (0.1)
Severe	0	0	0	0

Each value represents the mean (SEM) of the 16 patients in the study. *$P < 0.05$, †$P < 0.01$ *vs* baseline (paired *t*-test).

DISCUSSION

The results obtained in the present study clearly showed that in the majority of cases, HbA_{1c} levels improved after replacement of NPH with detemir. Mean basal insulin dose during each period after replacement increased significantly compared with NPH treatment, although this rise in basal insulin dose was observed without the severe hypoglycemic attacks that sometimes occurred during NPH administration. As shown in Table 3, detemir reduced the variability in FBG seen with NPH treatment. This stabilizing effect of detemir led to increased doses of detemir being given, with this desirable effect expected to result in significant decreases in FBG and HbA_{1c}. These beneficial effects might be a result of the fact that detemir is monophasic and is used without resuspension that might cause unstable pharmacokinetics, unlike NPH, which is biphasic and requires resuspension before injection. Another explanation for the desirable effects on FBG and HbA_{1c} might be detemir's ability to bind to albumin in the blood, resulting in prolonged metabolic action with lower peak levels than NPH.

In normal subjects, basal insulin constitutes approximately half of the daily insulin requirements[27]. It has been reported that basal–bolus therapy using the long acting insulin analogue, glargine, as basal insulin might result in good FBG control when the proportion of basal glargine is increased to 48% of the total insulin dose[28]. In the present study, we needed to increase this ratio of basal detemir dose to 36% in order to improve glycemic

Table 4 | Changes in the mean dose of daily basal and bolus insulin at baseline and during periods 1, 2 and 3 after replacing neutral protamine Hagedorn insulin with detemir

	Baseline	Period 1	Period 2	Period 3
		1–12 weeks	13–24 weeks	25–36 weeks
Basal insulin dose (IU/kg/day)	0.24 (0.03)	0.25 (0.03)	0.27 (0.03)*	0.28 (0.03)†
Bolus insulin dose (IU/kg/day)	0.51 (0.04)	0.50 (0.04)	0.49 (0.04)	0.48 (0.04)*
Total insulin dose (IU/kg/day)	0.75 (0.06)	0.75 (0.06)	0.76 (0.06)	0.75 (0.06)
Proportion of basal insulin (%)	30.6 (2.1)	32.3 (2.3)	34.4 (2.5)*	35.7 (2.6)†

The proportion of basal insulin represents the ratio of basal insulin dose divided by total insulin dose. Each value represents the mean (SEM) of the 19 patients in the study. *$P < 0.05$, †$P < 0.01$ *vs* baseline (paired *t*-test).

control. In addition, the majority of patients required increased doses of detemir to achieve better glycemic control. Based on these findings, we concluded it was not necessary to reduce the initial dose of detemir after replacement of NPH with detemir in Japanese patients with diabetes.

As shown in Table 5, replacement of NPH with detemir resulted in a significant increase in the frequency of overall and daytime hypoglycemic attacks, whereas the frequency of nocturnal attacks did not change. As blood glucose levels during the daytime are affected by food intake and bolus insulin injections, rather than basal insulin, which is usually given before bedtime, an increase in hypoglycemic attacks might be explained by a temporary excess dose of bolus insulin after improved FBG. Such cases are often experienced clinically during the transitional period of treatment modification. Therefore, hypoglycemic attacks can be controlled by reducing bolus insulin dose. In contrast, no severe hypoglycemic attacks that required another person's help to recover were observed throughout the study period. These findings showed that hypoglycemic attacks can be avoided during replacement protocols with detemir when both the basal and bolus amounts of insulin are taken into account.

Weight gain is a well-documented consequence of insulin treatment[22–24] and causes a dilemma for patients undergoing insulin therapy as increases in insulin dose might lead to a rise in bodyweight and a deterioration in glucose tolerance. In the present study, we showed that bodyweight did not increase after replacement of NPH with detemir, regardless of increases in detemir dose (Tables 2 and 4). In previously published reports[9–16], patients treated with detemir had less weight gain compared with patients treated with NPH. There are several possible explanations for this phenomenon that include the frequency of intermittent diet intake being reduced by fewer hypoglycemic attacks[11–14]; the high affinity of detemir to suppress hepatic glycogenesis[15,16,29]; detemir being transported across the blood–brain barrier and activating the insulin receptor signaling cascade causing neurological anorexia[15,16,30]; and detemir being less adipogenic compared with human insulin as a result of its lower affinity for the insulin receptor[31]. The present study also showed that bodyweight was reduced significantly by detemir treatment regardless of temporary increases in the frequency of hypoglycemic attacks. This result implies that the weight loss seen with detemir might not be the result of reduced calorie intake associated with fewer hypoglycemic attacks. In addition, our patients with weight loss commented that they felt a loss of appetite or were not in the mood to eat during detemir therapy. These observations suggest that detemir might have a neurological action to appestat that affects the central nervous system. It is also possible that a reduced dose of bolus insulin could explain the weight loss we observed. However, these are only hypothetical possibilities and further experiments are needed to establish the mechanism responsible for the reductions in bodyweight.

In many aspects, for instance increase in the dose of detemir and less weight gain, these results in the present study are consistent with those in the previous studies that compared detemir with NPH in basal–bolus therapy in subjects with type 1 diabetes[8,10–13]. These findings suggest the possibility that detemir has similar effects in Japanese patients as compared with Caucasian patients in clinical practice. The present results in Japanese patients with diabetes who had a low BMI (<23 kg/m^2) show that suppression of bodyweight caused by detemir administration was independent of BMI. In addition, FBG stabilized gradually week by week, and in some cases it took several weeks after replacement until the effect of detemir was expressed sufficiently. These observations of a concomitant and relative reduction in both within-patient variability in FBG and bodyweight should be regarded as beneficial clinical effects of detemir treatment.

A limitation of the present study was the relatively small sample size that was obtained in a single institution. Further studies of long term and a larger number of patients are required to validate these results. Continuous glucose monitoring systems (CGMS) are a new technology used clinically to measure blood glucose levels every 5 min over a 24-h period and allow visualization of the pattern of changes in blood glucose levels[32–35]. In the present study, the insulin dose was adjusted according to the results of SMBG recordings. However, this method takes several months to establish the optimal insulin dose of detemir. Although using CGMS would make it possible to adjust the dose of detemir in a shorter period, prolonged blood glucose monitoring by this technique has not yet gained widespread popularity. As conventional SMBG is used widely by patients to measure their blood glucose profile at home, the results of the present study should provide useful information for patients who have added detemir to their insulin regime.

The present report is a clinical study showing the usefulness of detemir therapy to improve glycemic control in Japanese patients with type 1 diabetes. In Japanese patients who received basal–bolus insulin therapy, administration of detemir as the basal insulin instead of NPH improved blood glucose control without a gain in bodyweight.

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