Insulin degludec is associated with less frequent and milder hypoglycemia in insulin-deficient patients with type 1 diabetes compared with insulin glargine or detemir

Shingo Iwasaki¹ · Junji Kozawa¹ · Takekazu Kimura^{1,2} · Kenji Fukui^{1,3} · Hiromi Iwahashi^{1,2} · Akihisa Imagawa¹ · Iichiro Shimomura¹

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Abstract

Introduction The aim of this study was to determine the efficacy of insulin degludec (IDeg) relative to insulin glargine (IGlar) or insulin detemir (IDet) in glycemic control, as evaluated by continuous glucose monitoring (CGM) in insulin-deficient patients with type 1 diabetes.

Methods We studied 28 outpatients treated with IGlar or IDet (IGlar/IDet). Basal insulin was switched to IDeg when glycemic control was considered unstable, as judged by the dawn phenomenon or nocturnal hypoglycemia. Whole-day CGM data were also divided into daytime and nighttime data.

Results The dawn phenomenon or nocturnal hypoglycemia under IGlar/IDet treatment was observed in all patients. Among 26 patients who completed the study, there were no significant differences in parameters representing glycemic variability, hyperglycemia, mean glycemic control, and HbA1c or insulin therapy-related quality of life at the night score. Measures of hypoglycemia [whole-day %Low and area under the curve (AUC) below 70] were significantly lower under IDeg treatment than under IGlar/IDet

treatment (%Low, 9.6 ± 11.5 vs. $14.7 \pm 14.9\%$, $p = 0.045$; AUC below 70, 85.5 ± 126.0 vs. 145.0 ± 178.6 mg/dl h, $p = 0.030$). Dividing patients into two groups according to percentage or degree of hypoglycemia under IGlar/IDet treatment, the whole-day, daytime and nighttime %Low in the high-percentage groups and AUC below 70 in the high-degree groups were significantly ameliorated, respectively ($p < 0.05$).

Conclusion Patients with unstable glycemic control under IGlar/IDet treatment did not improve glycemic control upon switching to IDeg, but the frequency and the degree of hypoglycemia was reduced in insulin-deficient outpatients with type 1 diabetes, especially in those suffering from severe hypoglycemia.

Keywords Degludec · Hypoglycemia · Glycemic variability · Type 1 diabetes

Introduction

Type 1 diabetes is characterized by insulin deficiency due to the loss of pancreatic beta cells [1]. The usual strategy for the treatment of type 1 diabetes is basal-bolus insulin therapy. This type of diabetes is also characterized by high variability in blood glucose levels and high frequency of hypoglycemia compared with those in type 2 diabetes [2–4].

Type 1 diabetic patients with diabetic microvascular complications have high glycemic variability [5]. Coronary artery calcification, a predictor of coronary events [6], is associated with glycemic variability in males with type 1 diabetes [7]. A history of severe hypoglycemic episodes is associated with a greater risk of dementia [8, 9]. Hypoglycemia is also associated with an increased risk of

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✉ Akihisa Imagawa
aimagawa@endmet.med.osaka-u.ac.jp

¹ Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, 2-2-B5 Yamadaoka, Suita 565-0871, Japan

² Department of Diabetes Care Medicine, Graduate School of Medicine, Osaka University, Suita, Japan

³ Department of Community Medicine, Graduate School of Medicine, Osaka University, Suita, Japan

cardiovascular disease events [10] and all-cause mortality [10–12] in insulin-treated patients with diabetes. Moreover, hypoglycemia is associated with driving accidents in patients with type 1 diabetes [13]. Therefore, insulin therapy that lowers glycemic variability and reduces the frequency of hypoglycemia is required for these patients. However, the dawn phenomenon and nocturnal hypoglycemia leading to the Somogyi effect are still often seen [14, 15].

Insulin degludec (IDeg) is a long-acting insulin analog, which is a preparation of soluble dihexamers that form stable and soluble multihexamers after subcutaneous injection [16]. IDeg has a terminal half-life of 25.4 h, twice that of insulin glargine (IGlar), and a duration of action of more than 42 h [17]. The day-to-day variability in the glucose-lowering effect of IDeg is one-fourth that of IGlar in patients with type 1 diabetes [18].

In previous reports, the frequency of nocturnal hypoglycemia has been shown to be reduced with IDeg treatment compared with IGlar or insulin detemir (IDet) treatment, whereas there is no significant difference of glycemic control indicators between these treatments [19–21]. In another study, the standard deviation (SD) and the coefficient of variation (CV) of the fasting plasma glucose (FPG) level have been found to be lower under IDeg treatment than under IGlar treatment in Japanese patients with type 1 diabetes [22]. In these studies, glycemic variability and hypoglycemia were evaluated by 7-point self-monitoring of blood glucose (SMBG) and not by continuous glucose monitoring (CGM). CGM is superior to SMBG, especially in detecting hypoglycemia unawareness and nocturnal hypoglycemia [23].

In the present study, we evaluated glycemic profiles by CGM in outpatients with type 1 diabetes. In patients with unstable glycemic control, judged on the basis of the dawn phenomenon or nocturnal hypoglycemia, we switched basal insulin from IGlar/IDet to IDeg. We compared glycemic variability, hyperglycemia, hypoglycemia and mean blood glucose level evaluated by CGM between IDeg treatment and IGlar/IDet treatment. We also analyzed clinical characteristics to detect parameters predicting the efficacy of IDeg.

Methods

Subjects

We studied 28 outpatients (10 males and 18 females) with type 1 diabetes at Osaka University hospital. Type 1 diabetes was diagnosed according to the criteria of the Japan Diabetes Society [24]. Participants included in the trial were patients with type 1 diabetes aged ≥ 20 years. Eligible participants had a known history of type 1 diabetes for at

least 6 months and had been treated for at least 6 months with a basal-bolus insulin regimen using IGlar or IDet (IGlar/IDet). The protocol excluded patients with clinically significant concomitant disease or severely impaired hepatic or renal function. Also excluded were patients with severe chronic heart failure (more than grade III in the NYHA classification), severe infection, heavy use of alcohol, perioperative status or other reasons leading to the physician in charge to judge that the patient was unsuitable for the study. Pregnant or breastfeeding women were also excluded. This study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of Osaka University and was registered with the University Hospital Medical Information Network (UMIN 000018430). Written informed consent was obtained from all participants before enrollment.

The patients enrolled in the study displayed the following characteristics (mean $\pm$ SD): 58.0 $\pm$ 10.7 years of age, 17.9 $\pm$ 12.1 years of duration of the disease, 22.4 $\pm$ 3.2 kg/m² body mass index (BMI) and 7.9 $\pm$ 1.0% (62 $\pm$ 10 mmol/mol) hemoglobin A1c (HbA1c). The fasting CPR levels, evaluated by chemiluminescent enzyme immunoassay, were <0.03 nmol/l in 25 patients, 0.13 nmol/l in 1 patient, 0.23 nmol/l in 1 patient and 0.33 nmol/l in 1 patient. The basal insulin dosage was 0.20 $\pm$ 0.08 U/kg/day. Twenty patients had been treated with IGlar (once a day in 12 patients and twice a day in 8 patients), and the remaining 8 patients had been treated with IDet (once a day in 3 patients and twice a day in 5 patients). Daily bolus insulin dosage was changeable according to carbohydrate consumption in 11 patients. In these patients, the carbohydrate-to-insulin ratio was 9.5 $\pm$ 3.6 (breakfast), 13.4 $\pm$ 4.5 (lunch) and 14.6 $\pm$ 4.2 (supper). The insulin therapy-related quality of life (QOL) at night (ITR-QOLN) questionnaire was evaluated in all the patients. The questionnaire consisted of 21 questions divided into 4 categories: anxiety before sleep (anxiety about nocturnal hypoglycemia before bedtime), disturbances during sleep (hypoglycemic disorder from bedtime to early morning), glycemic control before breakfast and overall well-being [25]. High scores indicated that QOL was good. The ITR-QOLN score in this study was 85.2 $\pm$ 23.7 points. According to their urinary albumin/creatinine ratio (ACR), the patients were classified into the following three groups of diabetic nephropathy: normoalbuminuria (ACR <30 mg/g creatinine), microalbuminuria ($30 \leq$ ACR <300 mg/g creatinine) and macroalbuminuria (300 mg/g creatinine $\leq$ ACR). Ophthalmologists assessed the presence of retinopathy through a dilated eye examination. Twenty patients were classified as having no evidence of diabetic retinopathy (NDR), five patients had simple diabetic retinopathy (SDR), and three patients had proliferative diabetic retinopathy (PDR). Diabetic

Table 1 Clinical characteristics of the patients

Characteristics	Patients
Sex (M/F) (<i>n</i>)	10/18
Age (years)	58.0 ± 10.7
Body mass index (kg/m ²)	22.4 ± 3.2
Duration of diabetes (years)	17.9 ± 12.1
HbA1c (%) (mmol/mol)	7.9 ± 1.0 (62 ± 10)
Fasting serum C-peptide (nmol/l) (<i>n</i>)	<0.03 (25), 0.13 (1), 0.23 (1), 0.33 (1)
Total daily insulin dose (U/kg/day) (<i>n</i>)	0.59 ± 0.17 (25)
Basal insulin dose (U/kg/day)	0.20 ± 0.08
Bolus insulin dose (U/kg/day) (<i>n</i>)	0.40 ± 0.11 (25)
Glargine/detemir (<i>n</i>)	20/8
Basal insulin injection once daily/twice daily (<i>n</i>)	15/13
ITR-QOLN (The insulin therapy related QOL at night) (score) (<i>n</i>)	85.2 ± 23.7 (26)
Nephropathy (normoalbuminuria/microalbuminuria/macroalbuminuria) (<i>n</i>)	24/2/2
Retinopathy (NDR/SDR/PDR) (<i>n</i>)	20/5/3
Neuropathy (negative/positive) (<i>n</i>)	19/9

Data are mean ± standard deviation

NDR no evidence of diabetic retinopathy, *SDR* simple diabetic retinopathy, *PDR* proliferative diabetic retinopathy

polyneuropathy was assessed according to the criteria of the Diabetic Neuropathy Study Group in Japan [26] and was positive for nine patients (Table 1).

Procedure

This study was performed in outpatients. The study design is outlined in Fig. 1. If the dawn phenomenon or nocturnal hypoglycemia was observed in the CGM data under IGLar/IDet treatment, we judged that glycemic control was unstable and switched basal insulin from IGLar/IDet to IDeg. If neither the dawn phenomenon nor nocturnal hypoglycemia was observed in the CGM data under IGLar/IDet treatment, we judged that glycemic control was stable and the patient was removed from the study. In this study, the dawn phenomenon was defined as an increase in the glucose level >20 mg/dl between 0:00 and 7:00 based on CGM data without antecedent hypoglycemia. Nocturnal hypoglycemia was defined as a blood glucose level of less than 70 mg/dl between 0:00 and 7:00 based on CGM data. Patients received IGLar/IDet either once or twice daily. When basal insulin was changed, IDeg was started once daily, and the dosage was adjusted by the attending physician throughout the study to achieve a FPG level below 130 mg/dl. The time when IDeg was administered was decided according to the attending physician's instruction. The type of bolus insulin preparation was not changed throughout the study, and the preprandial bolus insulin dosage

Fig. 1 Study design flowchart

was adjusted by each patient based on the attending physician's instructions. After 12 weeks, all patients underwent CGM for more than 24 h.

All patients underwent CGM in outpatient settings. Patients were asked to continue their usual daily life and to keep their lifestyles as similar as possible during CGM. Patients underwent CGM for more than 24 h with the CGMS Gold (Medtronic MiniMed, Northridge, CA, USA) or the CGMS ipro2 (Medtronic MiniMed). CGM was calibrated based on a minimum of four capillary blood glucose measurements per day. The recorded digital data on the CGMS Gold or the CGMS ipro2 were downloaded for further analysis using the MiniMed Solutions software program (Medtronic MiniMed, Northridge, CA, USA).

The following parameters were calculated from the CGM data: SD of the mean glucose value, measured over a 24-h period to assess intraday glycemic variability [27]; MAGE to assess the intraday glycemic variability [28] and to estimate the major peaks and valleys in the glucose profile, which is calculated as the mean height of excursions that are greater than 1 SD; *M* value to assess both the mean glucose value and the effect of glucose swings simultaneously, which is a logarithmic transformation of the deviation of glycemia from an arbitrarily assigned ideal glucose value [29], which was 100 mg/dl in this study; mean of daily differences (MODD) to assess interday

glycemic variability [30], which was calculated as the mean of the absolute differences between glucose values at the same time on 2 consecutive days and was analyzed in patients who underwent CGM for more than 40 h; area under the curve (AUC) above 180 and below 70 to assess the AUCs for glucose values over 180 mg/dl and under 70 mg/dl, respectively; %High and %Low to assess the percentages of time spent above 180 mg/dl and below 70 mg/dl, respectively; *J*-index to assess the quality of glycemic control based on the combination of information provided by the mean and the SD, calculated as $0.0019(\text{mean} + \text{SD})^2$ [31]; percentage coefficient of variation (%CV) to assess the ratio of the SD to the mean; high blood glucose index (HBGI) and low blood glucose index (LBGI) to assess the glycemic excursions, which suggest the risk of hyperglycemia or hypoglycemia according to an algorithm, respectively [32, 33]. The SD, MAGE, *M* value, MODD, *J*-index, %CV, HBGI and LBGI were all classified as parameters representing glycemic variability. AUC above 180 and %High were classified as parameters representing hyperglycemia. AUC below 70 and %Low were classified as parameters representing hypoglycemia. In addition to these parameters, the mean blood glucose level was calculated as a parameter representing mean glycemic control.

The data were divided into daytime (7:00–24:00) and nighttime data (0:00–7:00). %Low and AUC below 70 under IGLar/IDet treatment were also divided into high %Low and high AUC below 70 and Low %Low and Low AUC below 70 groups, with each group having the same number of patients.

Statistical analysis

We analyzed the change of the parameters evaluated by CGM and the change of the clinical parameters (BMI, HbA1c, total daily insulin dosage, bolus insulin dosage, basal insulin dosage) before and after switching basal insulin from IGLar/IDet to IDeg by using the paired *t* test, with the level of significance set at $p < 0.05$. All statistical analyses were performed with the JMP Pro 10.0.2 for Windows (SAS Institute, Cary, NC, USA). HbA1c values were converted to the National Glycohemoglobin Standardization Program (NGSP) equivalent values (%) in accordance with the official equation [34].

Results

Dawn phenomena or nocturnal hypoglycemia under IGLar/IDet treatment

The dawn phenomenon or nocturnal hypoglycemia under IGLar/IDet treatment was observed in all 28 patients

enrolled in this study (dawn phenomenon in 20 patients, nocturnal hypoglycemia in 16 patients, with both occurring in 8 patients). One patient withdrew. In accordance with the protocol, basal insulin in the remaining 27 patients was switched from IGLar/IDet to IDeg. One patient withdrew under the IDeg treatment, leaving 26 patients who completed the study. The clinical characteristics of the patients who completed the study are presented in Table S1. IDeg was administered in the morning in 11 patients, at noon in 1 patient, in the evening in 8 patients and at bedtime in 6 patients. There was no severe hypoglycemia requiring another person's assistance to restore blood glucose levels throughout the study.

Glycemic variability

There were no significant differences in parameters representing the whole-day glycemic variability evaluated by CGM between the IGLar/IDet treatment and the IDeg treatment (Table 2). There were no significant differences in parameters representing the daytime and nighttime glycemic variability (data not shown).

Hyperglycemia

There were no significant differences in parameters representing the whole-day hyperglycemia evaluated by CGM between the IGLar/IDet treatment and the IDeg treatment (Table 2). There were no significant differences in parameters representing the daytime and nighttime hyperglycemia (data not shown).

Hypoglycemia

Parameters representing the whole-day hypoglycemia, the whole-day %Low and AUC below 70 were significantly lower under IDeg treatment than under IGLar/IDet treatment (Table 2; Figs. 2a, 3a). The daytime and nighttime %Low and AUC below 70 were not significantly different between the IGLar/IDet treatment and the IDeg treatment (Table 2; Figs. 2b, c, 3b, c). When analyzing %Low in high and low subgroups, the whole-day, daytime and nighttime %Low in the high groups significantly decreased with IDeg treatment (the whole-day 26.0 ± 13.1 vs. $14.2 \pm 12.0\%$, $p < 0.001$; daytime 20.8 ± 15.4 vs. $10.4 \pm 10.0\%$, $p = 0.023$; nighttime 39.3 ± 16.6 vs. $22.2 \pm 22.2\%$, $p = 0.001$) (Fig. 4a, b, c). Similarly, when we analyzed AUCs below 70 in the high and low subgroups, the whole-day, daytime and nighttime AUC below 70 in the high groups significantly decreased with IDeg treatment (the whole-day 260.6 ± 187.9 vs. 139.9 ± 150.3 mg/dl h, $p = 0.012$; daytime 168.3 ± 119.4 vs. 71.8 ± 91.7 mg/dl h, $p = 0.020$; nighttime 113.5 ± 79.7 vs. 59.6 ± 75.5 mg/dl h, $p = 0.011$) (Fig. 5a, b, c). The

Table 2 Results of continuous glucose monitoring

	Insulin glargine or detemir (<i>n</i> = 26)	Insulin degludec (<i>n</i> = 26)	<i>p</i> value
Glycemic variability; whole day			
SD (mg/dl)	63.1 ± 20.0	61.7 ± 17.5	0.739
MAGE (mg/dl)	145.0 ± 44.8	144.9 ± 38.7	0.994
<i>M</i> value (mg/dl)	25.7 ± 16.3	24.5 ± 15.6	0.741
MODD (mg/dl)	62.7 ± 23.1	64.0 ± 22.2	0.824
<i>J</i> -index (mg/dl)	48.2 ± 22.5	49.0 ± 21.0	0.838
CV%	42.8 ± 12.5	40.3 ± 10.9	0.308
HBGI	10.9 ± 6.1	10.8 ± 5.3	0.942
LBGI	6.5 ± 5.6	5.4 ± 4.7	0.223
Hyperglycemia; whole day			
AUC above 180 (mg/dl h)	1179.2 ± 982.8	1238.2 ± 1097.8	0.785
%High (%)	31.0 ± 20.2	32.8 ± 20.6	0.572
Hypoglycemia			
%Low (%); whole day	14.7 ± 14.9	9.6 ± 11.5	0.045
%Low (%); daytime	11.3 ± 14.4	7.7 ± 9.3	0.181
%Low (%); nighttime	20.6 ± 22.4	16.0 ± 21.7	0.287
AUC below 70 (mg/dl h); whole day	145.0 ± 178.6	85.5 ± 126.0	0.030
AUC below 70 (mg/dl h); daytime	88.0 ± 116.6	47.6 ± 72.3	0.070
AUC below 70 (mg/dl h); nighttime	57.1 ± 79.7	38.0 ± 65.7	0.152
Mean glycemic control; whole day			
Mean (mg/dl)	149.9 ± 40.0	156.0 ± 36.8	0.354

Data are mean ± standard deviation

SD standard deviation, MAGE mean amplitude of glycemic excursions, MODD mean of daily differences, CV% coefficient of variation, HBGI high blood glucose index, LBGI low blood glucose index

whole-day, daytime and nighttime %Low and AUC below 70 in the low groups were not significantly different with IDeg treatment (the whole-day %Low 3.4 ± 4.2 vs. $5.1 \pm 9.4\%$, $p = 0.588$; daytime %Low 1.8 ± 1.8 vs. $5.1 \pm 8.0\%$, $p = 0.156$; nighttime %Low 1.9 ± 4.1 vs. $9.8 \pm 20.2\%$, $p = 0.195$; the whole-day AUC below 70 29.5 ± 47.0 vs. 31.0 ± 63.4 mg/dl h, $p = 0.948$; daytime AUC below 70 7.7 ± 10.4 vs. 23.1 ± 34.9 mg/dl h, $p = 0.086$; nighttime AUC below 70 0.75 ± 1.85 vs. 16.4 ± 47.8 mg/dl h, $p = 0.262$). The representative graph data of CGM under IDet and IDeg treatments in a patient who completed the study are shown in Figure S1. The representative graph data of CGM under IGlar and IDeg treatments in another patient are also shown in Figure S2. Figures S1 and S2 show the representative graph data from the high and low subgroups, respectively.

Mean glycemic control and HbA1c

Parameters representing mean glycemic control, the whole-day mean blood glucose level and HbA1c were not significantly different between the IGlar/IDet treatment and the IDeg treatment (Tables 2, 3). The daytime and nighttime mean blood glucose levels were not significantly

Fig. 2 Changes in %Low when basal insulin was switched from insulin glargine (IGlar) or detemir (IDet) to insulin degludec (IDeg). **a** Changes in whole-day %Low; **b** changes in daytime %Low; **c** changes in nighttime %Low. * $p < 0.05$ versus baseline (IGlar/IDet). n.s not significant

different between the IGlar/IDet treatment and the IDeg treatment (data not shown).

Fig. 3 Changes in AUC below 70 when basal insulin was switched from insulin glargine (IGlar) or detemir (IDet) to insulin degludec (IDeg). **a** Changes in whole-day AUC below 70; **b** changes in daytime AUC below 70; **c** changes in nighttime AUC below 70. * $p < 0.05$ versus baseline (IGlar/IDet). *n.s.* not significant

Fig. 4 Changes in %Low in the higher group when the subjects were divided into two subgroups of high and low %Low under IGlar/IDet treatment by the same number. **a** Changes in whole-day %Low; **b** changes in daytime %Low; **c** changes in nighttime %Low. * $p < 0.05$ versus baseline (IGlar/IDet). *n.s.* not significant

Insulin dosage

The total, bolus and basal insulin dosages were not significantly different between the IGlar/IDet treatment and the IDeg treatment (Table 3).

BMI

BMI values were not significantly different between the IGlar/IDet treatment and the IDeg treatment (Table 3).

Fig. 5 Changes in AUC below 70 in the higher group when the subjects were divided into two subgroups of high and low AUC below 70 under IGlar/IDet treatment by the same number. **a** Changes in whole-day AUC below 70; **b** changes in daytime AUC below 70; **c** changes in nighttime AUC below 70. * $p < 0.05$ versus baseline (IGlar/IDet). *n.s.* not significant

ITR-QOLN

The ITR-QOLN scores were not significantly different between the IDeg treatment and the IGlar/IDet treatment (Table 3). The ITR-QOLN score in the domain of anxiety before sleep tended to be higher with the IDeg treatment than with the IGlar/IDet treatment (Table 3).

Discussion

In this study, we evaluated glycemic profiles by CGM in insulin-deficient outpatients with type 1 diabetes and determined that glycemic control in all the patients was unstable under IGlar/IDet treatment. Patients who completed the study showed no significant differences in glycemic variability, hyperglycemia and mean glycemic control between the IDeg treatment and the IGlar/IDet treatment, consistent with results from a previous report [35]. We showed that whole-day hypoglycemia, represented by %Low and by AUC below 70, significantly decreased after switching basal insulin from IGlar/IDet to IDeg. In addition, by dividing patients into two groups according to the percentage and the degree of hypoglycemia under IGlar/IDet treatment, the measures of hypoglycemia (the whole-day, daytime and nighttime %Low and AUC below 70) in the high-percentage and the high-degree groups significantly improved. In the high %Low and high AUC below 70 group under IGlar/IDet treatment, the lowest glucose level in hypoglycemia

Table 3 Clinical parameters before and after switching from insulin glargine or detemir to insulin degludec

	Insulin glargine or detemir (<i>n</i> = 26)	Insulin degludec (<i>n</i> = 26)	<i>p</i> value
Body mass index (kg/m ²)	22.7 ± 3.1	22.8 ± 3.3	0.058
HbA1c (%) (mmol/mol)	7.9 ± 1.0 (62 ± 10)	7.9 ± 1.0 (61 ± 10)	0.774
Total daily insulin dose (U/kg) (<i>n</i> = 23)	0.59 ± 0.17	0.58 ± 0.16	0.165
Bolus insulin dose (U/kg) (<i>n</i> = 23)	0.40 ± 0.11	0.41 ± 0.13	0.501
Basal insulin dose (U/kg)	0.21 ± 0.08	0.20 ± 0.07	0.621
ITR-QOLN (score) (<i>n</i> = 24)	86.4 ± 24.2	89.6 ± 28.0	0.317
Anxiety before sleep	28.3 ± 10.6	31.3 ± 11.2	0.099
Disturbances during sleep	27.0 ± 9.9	28.4 ± 10.8	0.365
Overall well-being	19.9 ± 5.0	19.5 ± 5.1	0.667
Glycemic control before breakfast	11.1 ± 4.3	10.9 ± 4.8	0.723

Data are mean ± standard deviation

HbA1c hemoglobin A1c

significantly increased under IDeg treatment (data not shown). This increase might have reduced the time required for recovery from hypoglycemia, resulting in the improvement of the parameters representing hypoglycemia under IDeg treatment. This is the first report showing that the improvement in the frequency and severity of hypoglycemia under IDeg treatment depends on the severity of the hypoglycemia under IGLar/IDet treatment. Switching basal insulin from IGLar/IDet to IDeg might be especially effective in patients with type 1 diabetes who suffer from severe hypoglycemia.

Nighttime hypoglycemia was not significantly different between IGLar/IDet and IDeg treatment. This finding was inconsistent with those from previous studies and might be due to differences in the methods used to evaluate the frequency of hypoglycemia [19–21]. The frequency of hypoglycemia was evaluated as the percentage of time spent below 70 mg/dl using CGM in this study, whereas it was evaluated as the number of hypoglycemic episodes using SMBG in the previous studies [19–21]. Another possible reason for the inconsistency might be the different insulin dosage. The basal insulin dosage under IGLar/IDet treatment was significantly higher than that under IDeg treatment in the previous studies [19, 20]. Moreover, IDet was administered at bedtime [21], which might result in maximal insulin action at nighttime and therefore increase the frequency of nighttime hypoglycemia.

In this study, there were no significant differences in the mean daily blood glucose level, HbA1c or insulin dosage between the IDeg treatment and the IGLar/IDet treatment. The results of mean daily blood glucose level and HbA1c were consistent with those from a previous study of Japanese patients with type 1 diabetes [35], whereas the result of insulin dosage was inconsistent with previous studies [22, 35, 36]. Previously, IDeg was initiated at a dosage that

was reduced to ~80 to 90% of the total dosage of IGLar/IDet in the twice-daily group [32]. In contrast, in this study, the IDeg dosage in ten patients previously treated with twice-daily IGLar/IDet was adjusted according to the attending physician's judgment. These differences in the study design might explain the differences in insulin dosage.

This study has several limitations. First, the number of analyzed patients was relatively small. Second, performing CGM itself might partly cause the reduction of hypoglycemia. Previously, insulin therapy adjustments, in which insulin dosages were recalculated and redistributed based on the results of CGM, have been shown to reduce the incidence of hypoglycemic events in children with type 1 diabetes [37]. Because there was no algorithm for the titration of insulin dosages, we could not exclude the possibility that each attending physician's judgment might affect the results of our study. Finally, the present study was open-label in design and was a non-crossover trial using real-life conditions in which meals and activities could not be standardized. Therefore, a larger, double-blind crossover study would be recommended to confirm our results.

In conclusion, we showed that glycemic control was unstable in insulin-deficient outpatients with type 1 diabetes in this study. We also showed that whole-day hypoglycemia was significantly less frequent and milder under IDeg treatment than under IGLar/IDet treatment. Moreover, hypoglycemia was significantly improved in the groups that had a high percentage and a high degree of hypoglycemia under IGLar/IDet treatment. This study suggests that switching basal insulin from IGLar/IDet to IDeg might reduce the frequency and the degree of hypoglycemia in patients with type 1 diabetes, especially in patients suffering from severe hypoglycemia.

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Compliance with ethical standards

Conflict of interest I.S. received honoraria from Novo Nordisk as a speaker and received research funding from Sanofi and Eli Lilly. H.I. received research funding from Novo Nordisk and belongs to the department endowed by the companies including Novo Nordisk. None of the other authors have any conflicts of interest associated with this research.

Ethical standard This study was carried out in accordance with the Declaration of Helsinki of 1964 and later versions and approved by the ethics committee of Osaka University (approval no. 13089).

Informed consent Written informed consent was obtained from all participants before enrollment.

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