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ORIGINAL ARTICLE

Low fasting glucose-to-estimated average glucose ratio was associated with superior response to insulin degludec/aspart compared with basal insulin in patients with type 2 diabetes

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Keywords
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ABSTRACT

Aims/Introduction: The benefits of once-daily insulin degludec/aspart (IDegAsp) compared with basal insulin in type 2 diabetes patients have not been established.

Materials and Methods: This was a retrospective observational study. From a basal insulin cohort from three referral hospitals, patients were enrolled who initiated once-daily IDegAsp. A control group maintaining basal insulin was selected by propensity score matching. Glycated hemoglobin (HbA1c) changes over a period of 6 months and associated clinical factors were evaluated.

Results: The IDegAsp group and the control group comprised of 87 patients, respectively. Baseline HbA1c was comparable between the two groups (8.7 ± 0.9 vs 8.6 ± 0.9%, mean and standard deviation). After 6 months with matched insulin doses, HbA1c in the IDegAsp group was lower than that in the control group (8.1 ± 1.0 vs 8.4 ± 1.1%, $P = 0.029$). Among baseline variables, fasting plasma glucose (FPG) and fasting C-peptide in the IDegAsp were lower than that in the control (FPG 124.2 ± 38.4 vs 148.0 ± 50.6 mg/dL, $P < 0.001$). Considering that the lower FPG despite the comparable HbA1c could be related with the efficacy of IDegAsp, subgroup analysis was carried out according to a ratio of FPG-to-estimated average glucose, which is calculated from HbA1c. When compared with each control group, the superiority of IDegAsp in the reduction of HbA1c was significant only in the patients with a lower FPG-to-estimated average glucose ratio (0.49 ± 0.09), but not in those with a higher FPG-to-estimated average glucose ratio (0.79 ± 0.20).

Conclusions: We observed that IDegAsp was more effective than basal insulin in patients with an FPG lower than predicted by HbA1c, which might be related with insulin deficiency and postprandial hyperglycemia in patients on basal insulin therapy.

INTRODUCTION

Diabetes mellitus is a progressive disease[1]. Accordingly, in some patients with type 2 diabetes, as the duration of disease is prolonged, the insulin secretion ability of pancreatic β-cells decreases, and insulin administration is required[2]. Insulin therapy is usually initiated with basal insulin administration, and if

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glycemic control is still poor, the next treatment options include adding prandial insulin to basal insulin (basal–bolus insulin regimen) and converting to premixed biphasic insulin[3,4]. The basal–bolus insulin regimen would be the more physiological treatment[5]; however, it has the disadvantage of frequent injections[6]. Meanwhile, premixed biphasic insulin administration has an advantage of less frequent injections, but the risk of hypoglycemia increases[7].

Insulin degludec/insulin aspart (IDegAsp) complex is a newly developed premixed insulin, consisting of 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp)[8]. When injecting IDegAsp subcutaneously, IDeg forms stable multihexamer deposits, slowly releasing IDeg monomers and meeting basal insulin requirements. In the case of IAsp, it is circulated immediately after injection, and meets the mealtime insulin requirements[9]. Once-daily IDegAsp injection theoretically obtained the advantages of each regimen in part – providing both basal and one mealtime insulin in one shot, with less hypoglycemia than biphasic insulin[10].

Considering the characteristics of IDegAsp that can meet the basal and mealtime insulin requirements at once, once-daily IDegAsp can be expected to be more effective than basal insulin for blood glucose control. However, studies comparing the efficacy of once-daily IDegAsp and basal insulin have shown conflicting results. In a study comparing once-daily IDegAsp and insulin glargine (IGlar) in Japanese insulin-naïve type 2 diabetes patients, IDegAsp showed superior long-term glycemic control compared with IGlar[11]. In another study of patients with type 2 diabetes who had glycated hemoglobin (HbA1c) >7% on basal insulin administration and oral agents, once-daily IDegAsp was not inferior to IGlar in the reduction of HbA1c; however, once-daily IDegAsp induced a higher hypoglycemia rate than IGlar[12]. These results suggest that there is a subset of patients in whom once-daily IDegAsp is more beneficial than basal insulin, raising the issue of what would be the clinical characteristics associated with them.

Therefore, we preliminarily investigated 80 adults with type 2 diabetes who had switched to once-daily IDegAsp from basal insulin. We found the switching to IDegAsp reduced HbA1c at 3 months without significant insulin dose escalation, especially in patients with a lower fasting plasma glucose (FPG) relative to concurrent HbA1c[13]. However, it was a single-arm short-term study without a control group.

The present study was an extension study that extended the study period to 6 months, designating a control group under basal insulin administration by propensity score matching. As a result, we could obtain more solid real-world glycemic effects of once-daily IDegAsp compared with basal insulin in Korean patients with type 2 diabetes, along with clinical characteristics associated with efficacy of once-daily IDegAsp.

MATERIALS AND METHODS

Study participants

Clinical data of adults with type 2 diabetes who visited endocrinology outpatient clinics at Seoul National University Hospital, Seoul National Bundang hospital and Boramae Medical Center since February 2018, when the IDegAsp began to be prescribed, were retrospectively analyzed. We enrolled participants with type 2 diabetes with basal insulin (insulin glargine-U100, insulin glargine-U300, insulin detemir and insulin degludec) for at least 4 months, and HbA1c levels between 7 and 11%, and no changes in their oral hypoglycemic agents (total basal insulin cohort, $n = 324$). Among them, patients who switched to once-daily IDegAsp were set as the IDegAsp group, and the data were collected at the switch point (baseline), and after 6 months. From the total basal insulin cohort, those who maintained the basal insulin were selected as a control group using propensity score matching with age, sex, duration of diabetes, baseline HbA1c, estimated glomerular filtration rate, insulin dose and changes in insulin dose over a period of 6 months.

For further analysis about delta-FPG (ΔFPG), FPG, HbA1c and 2-h postprandial glucose (PP2) measurements were collected from patients with type 2 diabetes with basal insulin administration for >4 months from 2010 to 2019. The total number of patients whose data were available was 210 (PP2 cohort).

Calculation of estimated average glucose (eAG)[13]

$$eAG = 28.7 \times HbA1c(\%) - 46.7 (R^2 = 0.84,\ P < 0.0001)$$

Calculation of (ΔFPG)

Predicted fasting plasma glucose was estimated from a linear regression analysis between FPG and HbA1c in the total basal insulin cohort ($n = 324$), and used to calculate ΔFPG (Figure 4).

$$\text{Predicted} - \text{PG} = 12.6 \times \text{HbA1c}(\%) + 30,\ r = 0.262,\ p < 0.0001$$

$$\Delta FPG = \text{measured} - \text{FPG} - \text{predicted} - \text{FPG}$$

Outcomes

Primary outcomes were changes in HbA1c and FPG at 6 months after the switch from basal insulin to once-daily IDegAsp. Secondary outcomes were clinical factors associated with the efficacy of once-daily IDegAsp compared with basal insulin.

Statistical analysis

Continuous variables with a normal distribution were expressed as the mean and standard deviation, unless otherwise indicated. Variables between the IDegAsp and control groups were compared by Student's *t*-test, Mann–Whitney *U*-test and χ^2-test. Comparisons between the baseline and 6 months were carried out by paired *t*-test. The relationship between FPG and HbA1c in the total basal insulin cohort was analyzed by linear

regression analysis. The correlation between ΔFPG and other clinical variables was assessed through partial correlation analysis. *P*-values <0.05 were considered to show statistical significance. SPSS for Windows version 27.0 (IBM Corp., Armonk, NY, USA) and Prism 5 for Windows version 5.03 (GraphPad Software, San Diego, CA, USA) were used for the statistical analyses.

Ethical statement

The present study was carried out in accordance with the Declaration of Helsinki. The trial protocol was reviewed and approved by the institutional review board of each center (No. H-1903-068-1016, No. B-1905/540-406, No. 20190426/30-2019-35/053). The participants' consent was waived by the institutional review board, **as** this study used de-identified data.

RESULTS

Changes in HbA1c and FPG

A total of 324 participants were eligible for the total basal insulin cohort. Among them, 87 participants switched basal insulin to once-daily IDegAsp, and maintained this for >6 months. A total of 87 participants were matched for a control group (Figure 1). When comparing baseline characteristics between the IDegAsp and the control groups, FPG and C-peptide values were significantly lower in the IDegAsp group than the control group (FPG, 124.2 ± 38.4 vs 148.0 ± 50.6 mg/dL, $P < 0.001$; C-peptide, 1.50 ± 1.31 vs 2.04 ± 1.59 ng/mL, $P = 0.048$). Other baseline variables were not significantly different between the groups. In addition, significant insulin dose escalations over the 6-month study duration were comparable between the groups (0.033 ± 0.055 vs 0.033 ± 0.061 IU/kg, $P = 0.994$; Table 1).

Next, we compared HbA1c at 6 months and changes during the study period between the groups. We could observe that HbA1c was significantly lower in the IDegAsp group than the control group (8.1 ± 1.0 vs 8.4 ± 1.1%, $P = 0.029$; Figure 2a), and the reduction of HbA1C was also greater (−0.55 ± 0.78 vs −0.26 ± 1.02%, $P = 0.037$; Figure 2b). In the case of FPG, the 6-month measures showed significant difference between 2 groups (121.1 ± 37.8 vs 141.1 ± 42.1 mg/dL, $P = 0.001$; Figure 2c), with no significant changes during the 6 months in both the groups (Figure 2d).

To determine if the differences in FPG might have affected the favorable effect of IDegAsp on the HbA1c, propensity score matching was carried out again including baseline FPG, and the analysis results were the same (Table S1 and Figure S1).

Different glycemic benefits of IDegAsp according to FPG-to-eAG ratio

Because the baseline and 6-month FPG were significantly different between the groups despite the matched HbA1c, we hypothesized that discrepancy between FPG and HbA1c would be related with the IDegAsp efficacy. Because HbA1c showed the average glucose levels[14], we divided the IDegAsp group according to a ratio of FPG-to-average glucose estimated by HbA1c[14], and then each control was matched again from the total basal insulin cohort by propensity score matching. This time, baseline FPG was also included as a matching variable. Baseline characteristics of the subgroup pairs are presented in Table 2.

In the lower FPG/eAG ratio groups where the ratio was approximately 0.5 on average (Table 2), a significant HbA1c reduction was observed only in the IDegAsp group, but not in the control group (IDegAsp, from 8.7 ± 0.8 to 8.2 ± 1.0, $P < 0.001$; control, from 8.7 ± 0.9 to 8.5 ± 1.2%, $P = 0.495$; Figure 3a). The changes in HbA1c were significantly different between the IDegAsp and the control (−0.56 ± 0.80 vs −0.12 ± 1.24%, $P = 0.043$; Figure 3b).

Meanwhile, In the higher FPG-to-eAG ratio groups where the ratio was approximately 0.8 on average (Table 2), both the IDegAsp and the control groups showed significant decreases in HbA1c after 6 months (Figure 3c), with no statistical difference in the amount of HbA1c changes between the groups (Figure 3d).

Linear regression analysis between HbA1c and FPG in the total basal insulin cohort

From the subgroup analyses, a low FPG-to-eAG ratio was found to be tied to superiority of IDegAsp to basal insulin in HbA1c reduction. However, the estimation of eAG using HbA1c has not been confirmed in East Asians. In addition, the formula had been derived from various participants with type 1 diabetes, type 2 diabetes and without diabetes[14]. Therefore, to implement the present findings in clinical practice, we deduced a formula between FPG and HbA1c specifically in the patients with type 2 diabetes on basal insulin (total basal insulin cohort) using a regression analysis (Figure 4), and predicted FPG from a given HbA1c in the population on basal insulin.

Then, ΔFPG was calculated as described in the Materials and Methods section, which showed the gap between measured FPG and the predicted FPG. Lower ΔFPG values would suggest a lower FPG-to-eAG ratio, because both the predicted FPG and eAG are estimated by HbA1c.

Next, subgroup analyses were carried out as previously described, not according to the FPG-to-eAG ratio, but according to ΔFPG. The results (Table S2 and Figure S2) were the same with those analyses according to the FPG-to-eAG ratio (Table 2 and Figure 3).

Clinical interpretation of FPG-to-eAG ratio and ΔFPG

A low FPG-to-eAG ratio; that is, low FPG relative to concurrent HbA1c, would be interpreted as marked postprandial hyperglycemia. Therefore, we examined it in the PP2 cohort, where postprandial glucose levels were available among patients under basal insulin therapy (Figure 1). Glucose excursion after a meal calculated by (PP2 – FPG) / FPG was tied to a low FPG-to-eAG ratio, even after adjustment with age, sex, HbA1c and estimated glomerular filtration rate ($r = -0.547$, $P < 0.001$; Figure S3a). Among other variables, fasting C-peptide levels

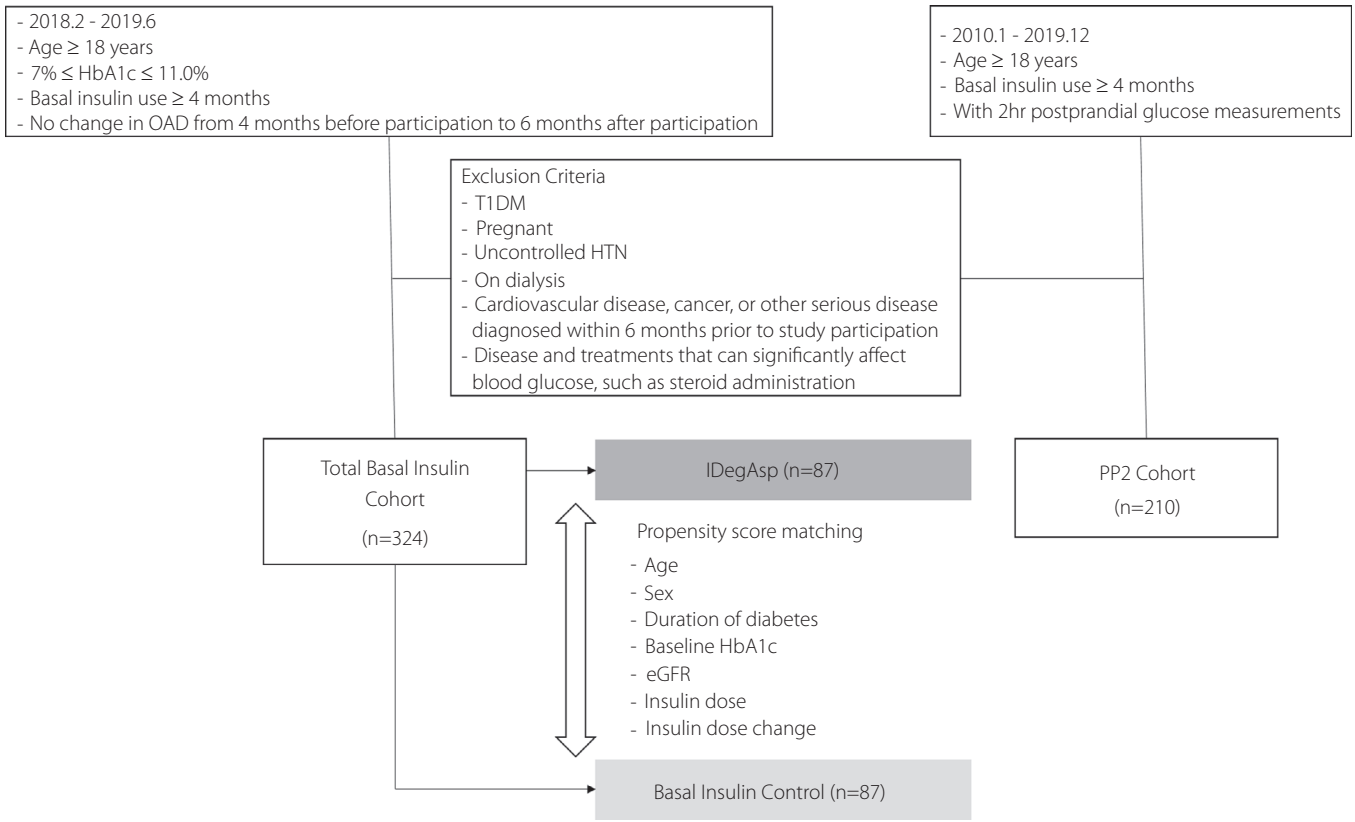

Figure 1 | Study population. eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HTN, hypertension; IDegAsp, insulin degludec/aspart; OAD, oral antidiabetic drug; PP2, 2-h postprandial glucose; T1DM, type 1 diabetes mellitus.

Table 1 | Clinical characteristics of the participants

Variables	IDegAsp (n = 87)	Control (n = 87)	P
Male sex, n (%)	45 (51.7)	44 (50.6)	0.879
Age (years)	68.7 ± 8.8	68.0 ± 10.2	0.662
BMI (kg/m^2)	24.6 ± 3.5	24.8 ± 3.6	0.632
Duration of diabetes (years)	19.6 ± 8.4	19.6 ± 9.5	0.982
Baseline HbA1c (%)	8.6 ± 0.9	8.7 ± 0.9	0.647
Baseline FPG (mg/dL)	124.2 ± 38.4	148.0 ± 50.6	<0.001
Baseline insulin dose (IU)	23.0 ± 9.0	23.4 ± 12.7	0.815
Change of insulin dose (IU/6 months)	2.2 ± 3.8	2.2 ± 4.6	0.986
Baseline insulin dose (IU/kg)	0.36 ± 0.13	0.36 ± 0.15	0.885
Change of insulin dose (IU/kg/6 months)	0.033 ± 0.055	0.033 ± 0.061	0.994
Fasting C-peptide (ng/mL)	1.50 ± 1.31 (n = 64)	2.04 ± 1.59 (n = 50)	0.048
eGFR (mL/min/1.73 m^2)	75.2 ± 25.5	77.2 ± 21.5	0.565
Basal insulin, n (%)			
Glargine U-100	46 (52.9)	59 (67.8)	0.177
Degludec	23 (26.4)	13 (14.9)	
Glargine U-300	13 (14.9)	12 (13.8)	
Levemir	5 (5.7)	3 (3.4)	

Values for categorical variables are presented as n (%); for continuous variables, as mean ± standard deviation. Statistical analysis was carried out using Student's t-test and χ^2-test. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDeg/Asp, insulin degludec/aspart.

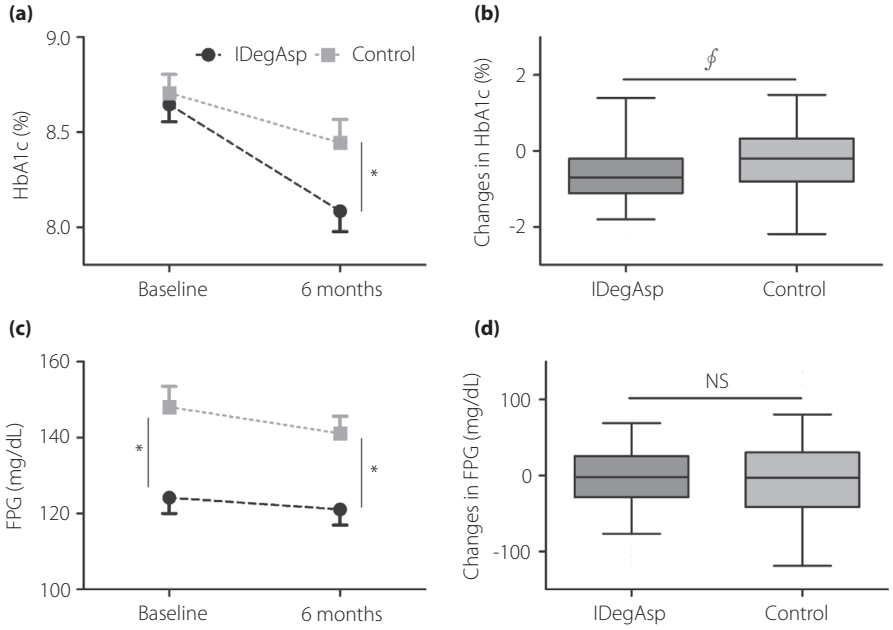

Figure 2 | Changes in glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) during the study period. Among patients with type 2 diabetes receiving basal insulin treatment, those who switched to once-daily insulin degludec/aspart (IDegAsp) were enrolled. A control group was set by propensity score matching among those who maintained basal insulin. HbA1c and FPG (a) before and (c) after the switch, and (b, d) the changes during the period were compared between the groups by a Student's *t*-test. Data are (a, c) means and the standard error of the mean, and (b, d) medians and the ranges (5–95%). *$P < 0.05$ between the IDegAsp and the control at each time point. ∮$P < 0.05$ between the IDegAsp and the control. NS, no statistical difference.

showed a significant correlation with the FPG-to-eAG ratio adjusted by age, sex, HbA1c and estimated glomerular filtration rate ($r = 0.196$, $P = 0.029$; Figure S3b). Those correlations were also observed with ΔFPG (Figure S3c,d).

DISCUSSION

In the present retrospective observational study of patients with type 2 diabetes, we found that changing to once-daily IDegAsp from basal insulin was effective in terms of HbA1c. Observation of different FPG along with comparable HbA1c between the IDegAsp and control groups, and further subgroup analyses showed that the superiority of IDegAsp was tied to as lower FPG-to-eAG ratio. The FPG-to-eAG ratio was negatively correlated with postprandial hyperglycemia, and positively correlated with fasting C-peptide, suggesting that severe insulin deficiency would contribute to the low FPG-to-eAG ratio and marked postprandial hyperglycemia, at least in part. ΔFPG, which was deduced from the total basal insulin cohort, showed the same associations.

Because it provides both basal insulin and bolus insulin, IDegAsp is expected to improve glycemic control by reducing fasting hypoglycemia and prandial hyperglycemia. Six prospective randomized controlled trials were published that compared once-daily IDegAsp with the basal insulin regimen using glargine or degludec, for a duration of 12–26 weeks[11,12,15–18]. Among the studies, the benefit of IDegAsp on the decrease of HbA1c was documented in just two of the studies[11,15]. Hypoglycemia was increased[12,17,18] or comparable[3,11,16] in the IDegAsp arms compared with the basal insulin arms. Some studies were carried out with insulin-naïve patients and some with patients on basal insulin; however, the results did not differ according to the participants. These results against the expected actions of IDegAsp suggest that IDegAsp should be prescribed in specific populations who can obtain the benefits of IDegAsp.

Then who are the right candidates for treatment with once-daily IDegAsp? In a recent review article dealing with practical use of IDegAsp, the authors suggested that patients with higher HbA1c levels (that is, higher eAG) in the context of normal pre-breakfast FPG levels had prandial hyperglycemia, and recommended reassessing the most suitable insulin regimen, including IDegAsp[19]. Indeed, we have already observed that patients who responded well to once-daily IDegAsp had those characteristics in a preliminary short-term study[13], and confirmed this in the current study. In addition, we identified that a low FPG-to-eAG ratio and low ΔFPG are actually associated with postprandial hyperglycemia (Figure S3a,c). Wang *et al.* also developed a linear regression between FPG and HbA1c in participants without diabetes, and showed that a HbA1c higher than predicted by FPG – a similar concept with low ΔFPG – was associated with post-challenge glycemic excursions[20]. It

Table 2 | Baseline characteristics of the subgroups according to fasting plasma glucose-to-estimated average glucose ratio

Variables	Lower FPG-to-eAG ratio (<0.60)			Higher FPG-to-eAG ratio (≥0.60)		
	IDegAsp (n = 48)	Control (n = 48)	P	IDegAsp (n = 39)	Control (n = 39)	P
Male sex, n (%)	23 (47.9)	17 (35.4)	0.214	22 (56.4)	21 (53.8)	0.820
Age (years)	69.8 ± 8.4	68.0 ± 8.2	0.292	67.3 ± 9.1	68.6 ± 10.5	0.535
BMI (kg/m^2)	24.5 ± 3.9	24.5 ± 3.4	0.986	24.6 ± 2.9	25.7 ± 3.4	0.110
Duration of diabetes (years)	19.6 ± 7.3	19.4 ± 10.1	0.930	19.5 ± 9.7	20.4 ± 9.6	0.697
Baseline HbA1c (%)	8.7 ± 0.8	8.7 ± 0.9	0.727	8.6 ± 0.9	8.6 ± 1.0	0.756
Baseline FPG (mg/dL)	96.6 ± 16.8	101.7 ± 22.8	0.219	158.1 ± 29.1	154.1 ± 42.7	0.632
FPG-to-eAG	0.48 ± 0.07	0.51 ± 0.10	0.094	0.81 ± 0.18	0.78 ± 0.22	0.560
Baseline insulin dose (IU)	22.0 ± 8.9	22.4 ± 10.7	0.844	24.2 ± 9.1	24.7 ± 10.0	0.794
Change of insulin dose (IU/6 months)	1.92 ± 3.00	1.67 ± 3.10	0.689	2.62 ± 4.57	2.77 ± 5.20	0.890
Baseline insulin dose (IU/kg)	0.35 ± 0.14	0.36 ± 0.15	0.768	0.37 ± 0.13	0.38 ± 0.15	0.853
Change of insulin dose (IU/kg/6 months)	0.030 ± 0.047	0.025 ± 0.050	0.602	0.038 ± 0.068	0.039 ± 0.059	0.980
Fasting C-peptide (ng/mL)	1.49 ± 1.65 (n = 32)	1.74 ± 1.38 (n = 25)	0.548	1.50 ± 0.90 (n = 32)	2.01 ± 1.61 (n = 21)	0.141
eGFR (mL/min/1.73 m^2)	70.8 ± 28.3	76.2 ± 26.4	0.340	80.5 ± 20.5	72.3 ± 22.4	0.095
Basal insulin, n (%)						
Glargine U-100	24 (50.0)	34 (70.8)	0.173	22 (56.4)	29 (74.4)	0.377
Degludec	16 (33.3)	11 (22.9)		7 (17.9)	3 (7.7)	
Glargine U-300	6 (12.5)	2 (4.2)		7 (17.9)	5 (12.8)	
Levemir	2 (4.2)	1 (2.1)		3 (7.7)	2 (5.1)	

Values for categorical variables are presented as n (%); for continuous variables, as mean ± standard deviation. Statistical analysis was carried out using Student's t-test and χ^2-test. BMI, body mass index; eAG, estimated average glucose; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

might be extrapolated to patients with type 2 diabetes[21]. Additionally, previous trials proved that once-daily IDegAsp was more effective than basal insulin in controlling postprandial glucose levels[15,17].

The two trials that showed HbA1c benefit of IDegAsp compared with basal insulin were carried out in Japan[11,15]. The participants of those trials did not have FPG lower than predicted by HbA1c levels. The present study in Korea, although a retrospective study, also showed HbA1c benefit. Other trials with results of just non-inferiority of IDegAsp were mainly carried out in Europe and the USA. Various factors could have affected this difference between the ethnicities. One factor might be more insulin deficiency in Asian people compared with the white people[22], as we observed that low FPG-to-eAG ratio and low ΔFPG were significantly associated with low fasting C-peptide (Figure S3b,d), suggesting severe insulin deficiency. However, it should be considered that C-peptide levels could decrease by administration of exogenous insulin[24]. Compatible with this speculation, in a study comparing impaired glucose tolerance and impaired fasting glucose, adults with isolated impaired glucose tolerance showed a more severe deficit in insulin secretion versus those with impaired fasting glucose alone, with insulin secretion as a dominant factor in impaired glucose tolerance[23]. Carbohydrate-rich Asian meals might be another reason.

The present study is novel in that it is the first real-world study about the efficacy of once-daily IDegAsp compared with a matched control of basal insulin, showing superior efficacy in HbA1c without significant a change in FPG, and providing indirect evidence that those who have marked prandial hyperglycemia and low insulin secretion would receive the benefit of the lowering of HbA1c by switching from basal insulin.

This was a retrospective study, and had a limitation in evaluating hypoglycemia, which is very important in insulin use. In addition, several trials (except the Japanese trials) reported that once-daily IDegAsp increased hypoglycemia compared with basal insulin. Inappropriate injection time of IDegAsp has been suggested as a reason for increased hypoglycemia, and injection before the largest meal has been recommended for efficacy and safety[12,19]. Regarding this issue, we should have analyzed the injection time in the current study; however it was not possible due to a lack of available records. Another point is the target fasting glucose levels. In two of three Japanese trials, target ranges were 90–130 mg/dL according to the Japanese Diabetes Society recommendations[25], whereas those in the other trials were 70–89 mg/dL. Lower target fasting glucose, along with a low-carbohydrate diet might result in increased hypoglycemia with IDegAsp injection, even before the largest meal.

Another limitation of the present study was that we could not assess insulin resistance. Besides insulin deficiency, insulin

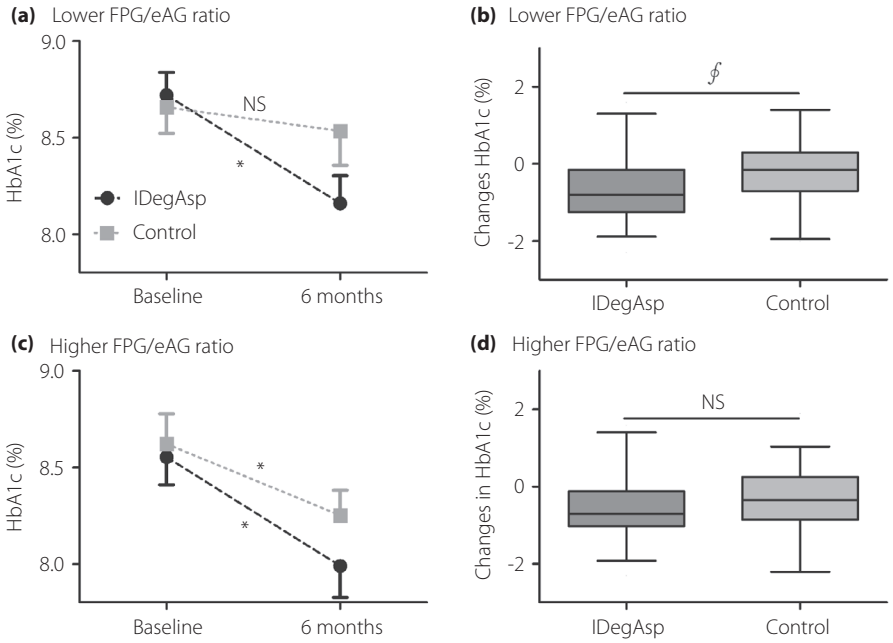

Figure 3 | Changes in glycated hemoglobin (HbA1c) in the subgroups according to fasting plasma glucose (FPG)-to-estimated average glucose (eAG) ratios. As the baseline and 6-month FPG were significantly different between the groups, we hypothesized that the discrepancy between FPG and HbA1c would be related with the insulin degludec/aspart (IDegAsp) efficacy. Therefore, the IDegAsp group was divided according to the FPG-to-eAG ratio, where eAG was calculated from HbA1c. Then each control was set by propensity score matching, including baseline FPG. (a, b) The FPG-to-eAG ratio was lower than 0.6. (c,d) The FPG-to-eAG was ≥0.6. HbA1c before and after the switch were analyzed by a paired *t*-test, and the changes during the period were compared between the groups by Student's *t*-test and Mann–Whitney *U*-test. Data are the (a) means and the (c) standard error of the mean, and (b) medians and (d) the ranges (5–95%). **P* < 0.05 between baseline and after 6 months within each group. ϕ*P* < 0.05 between the IDegAsp and the control. NS, no statistical difference.

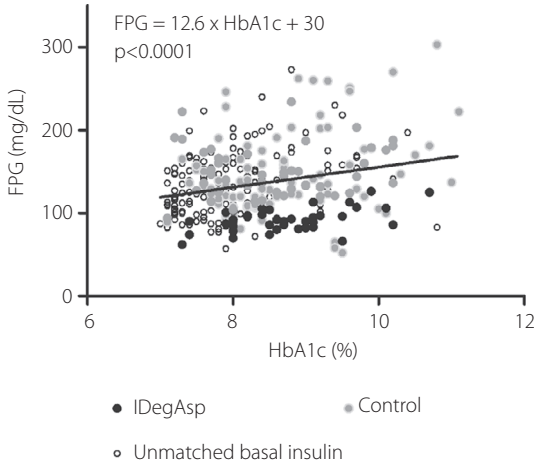

Figure 4 | A linear regression analysis between baseline glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG). A scattered graph showing FPG and HbA1c in the basal insulin cohort ($n = 324$). Linear regression analysis showed a significant correlation.

resistance is another component that determines postprandial hyperglycemia. For example, proteinuria can enhance insulin resistance and prandial hyperglycemia; however, not enough measurements were available in the basal insulin cohort.

Finally, although there was no statistic difference in the regimens of basal insulin between the groups (Table 1), there would be confounding effects caused by different pharmacokinetics of basal insulins[26–28]. A reviewer suggested that comparison between IDegAsp and IDeg would be equal, which could not be assessed in the current study due to the shortage of IDeg users.

To overcome the limitations and to obtain solid evidence for application of ΔFPG in the practical use of an insulin regimen, a prospective study is underway in patients with type 2 diabetes on basal insulin therapy, and with low ΔFPG as well; comparing once-daily IDegAsp and basal insulin using continuous glucose monitoring and glucose tolerance test, with regard to glycemic variability, and time in range, hypoglycemia, target fasting glucose, and HbA1c changes (KCT0004597).

In conclusion, we observed that once-daily IDegAsp was more effective in HbA1c reduction than basal insulin, especially in patients with lower FPG relative to concurrent HbA1c level. This seemed to show marked postprandial hyperglycemia. Insulin deficiency might contribute to these phenomena. The usefulness of ΔFPG in insulin intensification among patients with type 2 diabetes on basal insulin should be proved in further randomized controlled trials.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Changes in glycated hemoglobin and fasting plasma glucose after propensity score matching including fasting plasma glucose
Figure S2 | Changes in glycated hemoglobin in the subgroups according to Δfasting plasma glucose
Figure S3 | Clinical factors associated with fasting plasma glucose-to-estimated average glucose ratio and Δfasting plasma glucose
Table S1 | Clinical characteristics of the participants after propensity score matching including fasting plasma glucose
Table S2 | Baseline characteristics of the subgroups according to Δfasting plasma glucose values