JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Evaluation of safety of insulin degludec on undergoing total colonoscopy using continuous glucose monitoring

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Keywords
Continuous glucose monitoring, Insulin degludec, Total colonoscopy

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J Diabetes Investig 2015

doi: 10.1111/jdi.12409

Clinical Trial Registry
University Medical Information Network
UMIN000012265

ABSTRACT

Aims/Introduction: There is little information regarding how to use insulin degludec (D) when diabetic patients are preparing for total colonoscopy (TCS).

Materials and Methods: A total of 12 patients with type 2 diabetes treated with insulin D and scheduled to undergo TCS were enrolled in the present study. A continuous glucose monitoring device was attached to each patient for 4 days, from two evenings before TCS to the morning after the procedure. The patients fasted for 24 h, starting after 18.00 h the day before TCS. Insulin D was only discontinued the morning of the day TCS was carried out.

Results: No patients experienced hypoglycemia during the daytime fasting period (08.00–18.00 h the day of TCS); the hypoglycemic index, mean glucose level, and standard deviation were 0, 141.3 ± 31.5 mg/dL and 15.6 ± 6.5 mg/dL. The mean glucose level and standard deviation during the daytime fasting period were significantly lower than during the daytime control period (08.00–18.00 h the day before TCS; $P = 0.003$, $P = 0.001$, respectively). The mean fasting glucose and fasting plasma glucose levels were significantly correlated ($r = 0.78$, $P = 0.002$), as were both the mean glucose level and standard deviation during the daytime control period, and the change in the mean glucose level (fasting period minus control period; $r = –0.79$, $P = 0.002$, and $r = –0.69$, $P = 0.01$, respectively).

Conclusions: Patients can safely undergo TCS when insulin D is discontinued only once on the day of the procedure.

INTRODUCTION

A significant correlation between diabetes and the risk of colon cancer has been reported[1]. Therefore, screening for colon cancer with total colonoscopy (TCS) in patients with type 2 diabetes is important. Although the gold standard for diagnosis of colon cancer is TCS[2], bowel preparation for this procedure is sometimes cumbersome for patients with diabetes. Because most patients undergoing TCS are required to fast for a long period except for intake of bowel lavage solution, which does not have any calories, use of agents with hypoglycemic action should be reduced or discontinued during preparation for TCS. In this scenario, glucose variability in patients with diabetes taking these antidiabetic agents might be poorer. Furthermore, in patients taking agents with a long-acting profile, hypoglycemia could consistently occur even with discontinuation of these agents.

Insulin degludec (D), which is an ultralong-acting insulin analog, has been available clinically in Japan since March 2013. Insulin D can achieve both less glucose variability and a lower frequency of hypoglycemia even in unstable patients with diabetes, because it provides a stable insulin concentration for more than 42 h[3]. Recently, we reported that the action profile of insulin D is beneficial for glycemic control at night-time, when patients are fasting[4]. When preparing to undergo TCS, most patients are required to fast both the night before and the day of the procedure. Theoretically, when the dose of insulin D is appropriate as basal insulin, even if patients treated with insulin D are fasting, hypoglycemia is not supposed to occur because of its pharmacological characteristics[5]. However, there

Received 11 February 2015; revised 23 July 2015; accepted 28 July 2015

are some concerns that patients treated with insulin D might develop hypoglycemia if the fasting period is extended during the day of the procedure, because the effect of this insulin continues for more than 42 h. In such a situation, we have only limited experience in using insulin D, and there is little information available regarding how to use insulin D. In the present study, we evaluated safety in patients with type 2 diabetes treated with insulin D and scheduled to undergo TCS by measuring glucose variability with continuous glucose monitoring (CGM).

MATERIALS AND METHODS

Patients with type 2 diabetes who were treated with the same dose of insulin D for more than 3 months were encouraged to undergo TCS for screening of colon cancer from December 2013 to January 2014, and we consecutively and prospectively enrolled patients who agreed to the procedure. On admission, a CGM device (Medtronic ipro2; Medtronic MiniMed, Northridge, CA, USA) was attached to each patient for 4 days, from two evenings before (the first day) undergoing TCS to the morning after the procedure (the fourth day), and glucose variability was evaluated. On the day before the procedure (the second day), patients were treated with their usual dose of insulin, and consumed test meals at 08.00, 12.00 and 18.00 h. Purgatives (Sennoside A&B calcium and sodium picosulfate hydrate) were given at 22.00 h. On the day TCS was carried out (the third day), the patients consumed polyethylene glycol electrolyte solution (1 L) and water (500 mL) within a 2-h period starting at 10.00 h. TCS was carried out at 16.00 h to integrate procedure time, because the time required for the bowel cleaning was routinely up to 6 h, and the patients consumed a test meal at 18.00 h. By following this protocol, the patients fasted for 24 h. Neither glucagon nor any anticholinergic agent was given to the patients to suppress bowel movement before or during colonoscopy. Insulin D was injected at 08.00 h every morning except the third day (the day TCS was carried out), and patients discontinued treatment with all antidiabetic agents only at breakfast and lunch on the third day (the day TCS was carried out). The patients were given three meals per day, each with 1,440, 1,600 or 1,840 kcal, determined according to their physique[6]. Identical test meals were given to each patient based on the recommendation of the Japan Diabetes Society. The patients did not have any special meal, such as a low-residue diet, on the day before colonoscopy. The physical activity at admission to the study was 1.5 metabolic equivalents based on the analysis of baseline data. Patients with severe renal dysfunction (serum creatinine level ≥2.0 mg/dL) or judged to be unsuitable for participation for medical reasons, were excluded from this study.

The primary aim of the present study was to evaluate the safety of insulin D by measuring the frequency of cases of hypoglycemia (<70 mg/dL), the hypoglycemic index[7], and the mean glucose level and standard deviation (SD)[8] during the daytime fasting period (fasting between 08.00 and 18.00 h on the day of TCS). These parameters were also compared between the daytime fasting period and daytime control period (non-fasting between 08.00 and 18.00 h on the day before TCS), and the relationships of the change in the mean glucose level (daytime fasting period – daytime control period) with the mean glucose level during the daytime control period and SD during the daytime control period were determined.

Data are shown as mean and SD. Statistical analysis was carried out with Welch's *t*-test, χ^2-test, paired *t*-test and Pearson's correlation coefficient test. A *P*-value of <0.05 was considered significant. The study protocol was approved by the Ethical Committee of Ichinomiyanishi Hospital (authorization no. 25017), and was registered in a clinical trial database with the University Medical Information Network (no. UMIN000012265).

RESULTS

Baseline characteristics of patients

A total of 12 patients (8 men and 4 women) were enrolled in the present study. The baseline characteristics included age of 65.6 ± 11.3 years, body mass index of 23.7 ± 2.6 kg/m^2, glycated hemoglobin of 7.2 ± 0.8% (54.7 ± 8.4 mmol/mol), duration of diabetes of 18.0 ± 14.2 years, fasting plasma glucose (FPG) level of 135.6 ± 44.8 mg/dL and C-peptide index (CPI; =fasting C-peptide immunoreactivity/FPG × 100) of 0.9 ± 0.6. Six patients received basal–bolus treatment (basal–bolus), and six patients received basal insulin only (basal). The basal insulin dose was 0.19 ± 0.08 U/kg/day, and the total insulin dose was 0.31 ± 0.18 U/kg/day. The total insulin dose was significantly higher in the basal–bolus group than in the basal group. In regard to oral antidiabetic agents, dipeptidyl peptidase-4 inhibitors were used in significantly more patients in the basal group compared with the basal–bolus group. Significantly more female patients were in the basal–bolus group compared with the basal group. There were no other significant differences in characteristics between the two groups. A colon adenoma (diameter of 20 mm) was detected in one of the 12 patients and resected successfully. The performance time of TCS was 20.8 ± 9.5 min (Table 1).

Primary findings

Evaluation of the 12 Patients

No patients experienced hypoglycemia during the daytime fasting period; the hypoglycemic index, mean glucose level, and SD were 0, 141.3 ± 31.5 and 15.6 ± 6.5 mg/dL, respectively (Figure 1a and Table 2). The mean glucose level during the daytime fasting period and the FPG level were significantly correlated ($r = 0.78$, $P = 0.002$; Figure 2). There were no significant differences between the mean glucose level during the daytime fasting period and the FPG level (141.3 ± 31.5 vs 135.6 ± 44.8, $P = 0.49$).

Evaluation of Each Insulin Regimen

No patients in the basal–bolus group experienced hypoglycemia during the daytime fasting period; the hypoglycemic

Table 1 | Baseline characteristics of patients

Characteristic	Overall	Basal–bolus	Basal	*P* (b vs c)
n (male/female)	12 (8/4)	6 (2/4)	6 (6/0)	$P_2 = 0.01$
Age (years)	65.6 ± 11.3	62.8 ± 15.0	68.3 ± 6.2	$P_1 = 0.43$
Duration of diabetes (years)	18.0 ± 14.2	18.0 ± 14.8	18.0 ± 15.1	$P_1 = 1$
BMI (kg/m^2)	23.7 ± 2.6	22.6 ± 2.5	24.8 ± 2.3	$P_1 = 0.15$
HbA_{1c}, NGSP (%)	7.2 ± 0.8	7.5 ± 0.9	6.9 ± 0.4	$P_1 = 0.19$
HbA_{1c}, IFCC (mmol/mol)	54.7 ± 8.4	58.1 ± 10.3	51.4 ± 4.7	$P_1 = 0.19$
Basal insulin dose (U/kg/day)	0.19 ± 0.08	0.23 ± 0.07	0.15 ± 0.07	$P_1 = 0.09$
Total (basal and bolus) insulin dose (U/kg/day)	0.31 ± 0.18	0.46 ± 0.10	0.15 ± 0.07	$P_1 = 0.0002$
FPG (mg/dL)	135.6 ± 44.8	147.0 ± 58.2	124.2 ± 26.9	$P_1 = 0.41$
CPI	0.9 ± 0.6	0.7 ± 0.6	1.1 ± 0.4	$P_1 = 0.17$
Injection time of basal insulin	08.00 h			
Sulfonylurea agent (*n*)	0	0	0	$P_2 = 1$
Biguanide agent (*n*)	6	2	4	$P_2 = 0.25$
Thiazolidine (*n*)	0	0	0	$P_2 = 1$
α-Glucosidase inhibitor (*n*)	2	2	0	$P_2 = 0.12$
DPP4 inhibitor (*n*)	8	2	6	$P_2 = 0.01$
GLP-1 analog (*n*)	0	0	0	$P_2 = 1$
Insulinotropic agent with rapid onset (*n*)	0	0	0	$P_2 = 1$

Data are shown as mean ± standard deviation. *P*, basal–bolus vs basal; P_1, Welch's *t*-test; P_2, χ^2-test. Basal, basal insulin only; Basal–bolus, basal–bolus treatment; BMI, body mass index; CPI, C-peptide index (=fasting C-peptide immunoreactivity/FPG × 100); DPP, dipeptidyl-peptidase; FPG, fasting plasma glucose; GLP, glucagon-like peptide; HbA_{1c}, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program; SD; standard deviation.

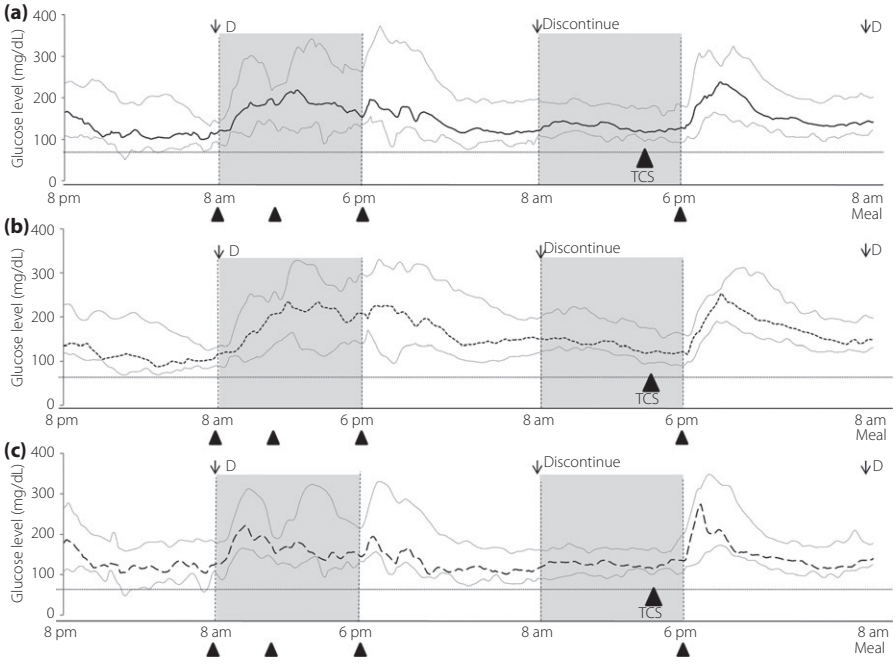

Figure 1 | Glucose variability on continuous glucose monitoring in patients during treatment with insulin degludec. Values represent median (thick lines) and interdecile ranges (fine lines). (a) Overall (*n* = 12). (b) Basal–bolus treatment (*n* = 6). (c) Basal (basal insulin only; *n* = 6). (d) Insulin degludec. TCS, total colonoscopy.

index, mean glucose level, and SD were 0, 146.0 ± 39.0 and 17.2 ± 6.0 mg/dL, respectively. In addition, no patients in the basal group experienced hypoglycemia; the hypoglycemic index, mean glucose level, and SD were 0, 136.6 ± 24.5 and 14.1 ± 7.1 mg/dL, respectively (Figure 1b,c and Table 2).

Table 2 | Parameters of glucose variability in patients treated with insulin degludec during the daytime control period and daytime fasting period

	Overall		*P*	Basal–bolus		*P*	Basal		*P*
	Daytime control period	Daytime fasting period		Daytime control period	Daytime fasting period		Daytime control period	Daytime fasting period	
Hypoglycemic index	0	0	1	0	0	1	0	0	1
Mean glucose level (mg/dL)	191.0 ± 50.8	141.3 ± 31.5	0.003	194.4 ± 53.9	146.0 ± 39.0	0.09	187.7 ± 52.4	136.6 ± 24.5	0.02
SD (mg/dL)	43.0 ± 20.1	15.6 ± 6.5	0.001	47.1 ± 19.4	17.2 ± 6.0	0.02	38.9 ± 21.8	14.1 ± 7.1	0.06

Data are shown as mean ± standard deviation (SD). *P*, paired *t*-test. Daytime control period, daytime non-fasting control period (non-fasting between 08.00 and 18.00 h on the day before total colonoscopy); Daytime fasting period, daytime fasting period (fasting between 08.00 and 18.00 h on the day before total colonoscopy).

Secondary findings

Comparison of Parameters Between the Daytime Fasting Period and Daytime Control Period

Evaluation of the 12 patients

No patients experienced hypoglycemia during the daytime control period, and the hypoglycemic index was 0. There were no significant differences in the hypoglycemic index between the daytime fasting period and daytime control period. The mean glucose level and SD during the daytime fasting period were significantly lower than those during the daytime control period ($P = 0.003$ and $P = 0.001$, respectively; Figure 1a and Table 2).

Evaluation of each insulin regimen

No patients in the basal–bolus group experienced hypoglycemia during the daytime control period, and the hypoglycemic index was 0. There were no significant differences in the hypoglycemic index between the daytime fasting period and daytime control period. The mean glucose level during the daytime fasting period tended to be lower than that during the daytime control period ($P = 0.09$). The SD during the daytime fasting period was significantly lower than that during the daytime control period ($P = 0.02$; Figure 1b and Table 2).

Similarly, no patients in the basal group experienced hypoglycemia during the daytime control period, and the hypoglycemic index was 0. There were no significant differences in the hypoglycemic index between the daytime fasting period and daytime control period. The mean glucose level during the daytime fasting period was significantly lower than that during the daytime control period ($P = 0.02$). The SD during the daytime fasting period tended to be lower than that during the daytime control period ($P = 0.06$; Figure 1c and Table 2).

Estimation of the relationship between the mean glucose level during the daytime control period and the change in the mean glucose level

The mean glucose level during the daytime control period and the change in the mean glucose level were significantly correlated ($r = -0.79$, $P = 0.002$; Figure 3a), although the mean glucose level during the daytime control period was not significantly correlated with the total insulin dose or CPI (Figure 3b,c).

Estimation of the relationship between the SD during the daytime control period and the change in the mean glucose level

The SD during the daytime control period and the change in the mean glucose level were significantly correlated ($r = -0.69$, $P = 0.01$; Figure 4a), although the SD during the daytime control period was not significantly correlated with the total insulin dose or CPI (Figure 4b,c).

DISCUSSION

Patients undergoing TCS are often required to fast for nearly 20 h, and occasionally for a full 24 h because both breakfast

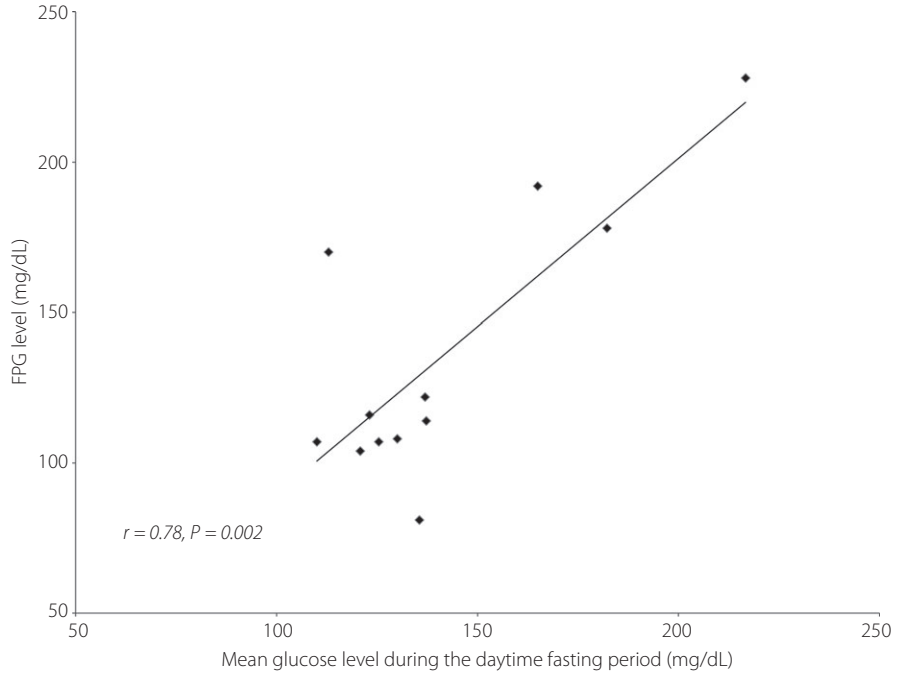

Figure 2 | Figure showing a significant correlation between the mean glucose level during the daytime fasting period and the fasting plasma glucose (FPG) level (r = 0.78, P = 0.002, Pearson's correlation coefficient test [n = 12, r = 0.58]). Daytime fasting period, daytime fasting period (fasting between 08.00 and 18.00 h on the day of total colonoscopy).

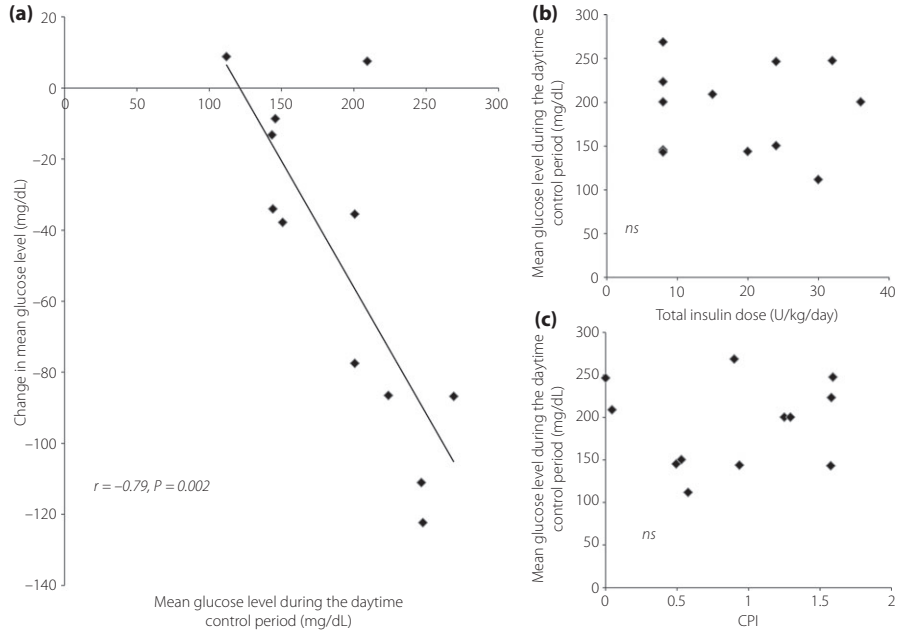

Figure 3 | (a) A significant correlation between the mean glucose level during the daytime control period and the change in the mean glucose level (daytime fasting period – daytime control period; r = –0.79, P = 0.002, Pearson's correlation coefficient test [n = 12, r = 0.58]). Daytime control period, daytime non-fasting control period (non-fasting between 08.00 and 18.00 h on the day before total colonoscopy). (b) The lack of any significant correlation between the total insulin dose and the mean glucose level during the daytime control period. (c) The lack of any significant correlation between the C-peptide index (CPI; =fasting C-peptide immunoreactivity/FPG × 100) and the mean glucose level during the daytime control period.

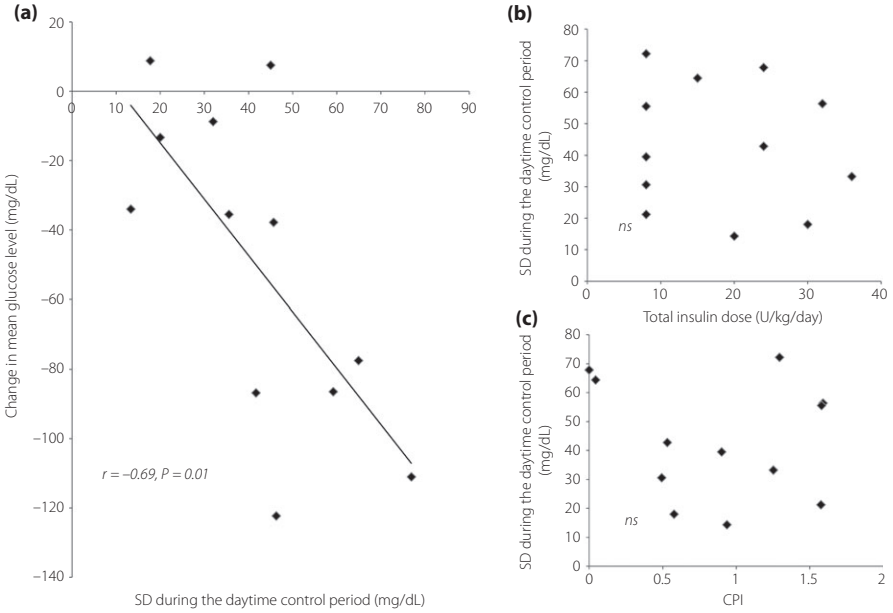

Figure 4 | (a) A significant correlation between the standard deviation (SD) during the daytime control period and the change in the mean glucose level ($r = -0.69$, $P = 0.01$, Pearson's correlation coefficient test [$n = 12$, $r \geq 0.58$]). (b) The lack of any significant correlation between the total insulin dose and the SD during the daytime control period. (c) The lack of any significant correlation between the C-peptide index (CPI) and the SD during the daytime control period.

and lunch are skipped to allow for preparation for TCS. This is a cumbersome issue for diabetic patients who are treated with agents with hypoglycemic action, especially long-acting insulin D. In the present study, we investigated safety in patients with type 2 diabetes treated with insulin D and scheduled to undergo TCS by measuring glucose variability with CGM. Although there was concern that hypoglycemia would occur during the daytime fasting period (24–34 h after the last injection of insulin D), none of the patients in the present study experienced hypoglycemia during this time, even though they were fasting and skipped only one dose of insulin D on the day TCS was carried out. Furthermore, we confirmed that glucose variability was minor, and the mean glucose level during the daytime fasting period was stable and at nearly the same level as the FPG. Similarly, on evaluation of glucose variability in the basal–bolus and basal groups, we found no difference between the insulin regimens. This suggested that the effect of insulin D persisted for more than 24 h, and remained stable and safe until at least 34 h after the last injection. This is because insulin D is present as a dihexamer in pharmaceutical preparations; after subcutaneous injection, insulin D lodges in the subcutaneous tissue temporarily as a multihexamer. Subsequently, insulin D converts into the monomer gradually, and is absorbed into the bloodstream slowly and continuously. We believe that this mechanism enables a stable blood insulin concentration of insulin D, and achieves stable and safe blood glucose regulation[9].

However, the 'carryover effect' of insulin D means that the effect beyond 24 h can vary, depending on the level of glycemic control of each patient on the previous day. As a result, in patients with comparatively low glucose control on the previous day, the carryover effect of insulin D could cause hypoglycemia during the daytime fasting period. Conversely, in patients who are in hyperglycemia, the effect of insulin D might be insufficient. Therefore, we evaluated the relationship between the mean glucose level during the daytime control period and the change in the mean glucose level (daytime fasting period − daytime control period). Our findings showed that the mean glucose level and SD during the daytime control period were both significantly correlated with the change in the mean glucose level. In patients with higher glucose levels or wider glycemic variability, the mean glucose level during the daytime fasting period might be subject to greater decreases or wider fluctuation. In view of the correlation between the mean glucose level during the daytime fasting period and the FPG level, which was observed in the present study, the mean glucose level during the daytime control period might decrease to the FPG level in most patients, independent of the mean glucose level or SD. Although the present study was not designed to evaluate the causes of the observed association, it is likely that the pharmacokinetic properties of insulin D contributed to this observed effect, as the mean glucose level or SD during the daytime control period did not depend on the exogenous insulin dose or CPI, which is indicative of an endogenous insulin secretory capacity[10].

Insulin D has the following pharmacological characteristics[5]. First, there is a carryover effect, which continues from 24 to 42 h, overlaps for a couple of days and reaches steady state. Second, in steady state, there is little difference between peak and

trough concentrations. Third, once the concentration becomes steady state, the effect would maintain appropriate glycemic control if the daily insulin dose were comparable with daily insulin consumption; if not, glycemic control would be unstable. For these reasons, in the present study, stable and appropriate glycemic control seems to have been achieved during the daytime fasting period, because almost all patients were in steady state of insulin D concentration and had a good FPG level; furthermore, one dose of insulin was equivalent to the daily intake of insulin in each patient. Thus, we consider that insulin D can maintain stable and appropriate glycemic control during the daytime fasting period as long as two meals (breakfast and lunch) and one dose of insulin are simultaneously discontinued.

Recent reports have shown increasingly stronger links between diabetes and several types of gastroenterological cancers, such as colon cancer[1], hepatoma[11,12] and pancreatic cancer[13,14], so it is desirable for more diabetic patients to undergo routine screening for these cancers. Gastrointestinal endoscopy, abdominal ultrasonography, contrast-enhanced computed tomography and other imaging methods are often used widely for screening. Unfortunately, if malignant lesions are found, patients need to undergo surgical procedures or chemotherapy. Because patients are often required to fast for these examinations or treatments, even if they are treated with long-acting insulin, such as insulin D, a reduction or discontinuation of a dose of insulin might be unavoidable. Therefore, treatment of malignant disease in patients with diabetes is cumbersome, because frequent modification of doses of insulin aggravates glycemic control[15]. In the present study, we showed that insulin D can maintain appropriate glycemic control during fasting without additional regulation of insulin as long as insulin D is only discontinued once in patients with stable glycemic control. This finding could provide beneficial information for the treatment of patients with diabetes. However, hypoglycemia can occur occasionally in patients with long-acting basal insulin during a long fast period, in cases of overdose compared with insulin practical requirement. We should be careful about hypoglycemia whenever diabetic patients are exposed to a long fast period.

However, some limitations to the present study, such as the observational study design and small sample size, preempt the drawing of any definitive conclusions regarding the safety of insulin D. Based on this pilot study, a prospective clinical study is planned to elucidate this pharmaceutical effect compared with that of insulin glargine.

DISCLOSURE

The authors declare no conflict of interest.

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