Is it possible to predict the onset of nocturnal asymptomatic hypoglycemia in patients with type 1 diabetes receiving insulin degludec? Potential role of previous day and next morning glucose values

Hiroshi Takahashi*, Rimei Nishimura
Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Keywords
Continuous glucose monitoring, Nocturnal asymptomatic hypoglycemia, Type 1 diabetes

*Correspondence
Hiroshi Takahashi
Tel.: +81-3-3433-1111 ext. 3249
Fax: +81-3-3578-9753
E-mail address: hiro6117@jikei.ac.jp

J Diabetes Investig 2021; 12: 365–373
doi: 10.1111/jdi.13363

ABSTRACT
Aims/Introduction: To determine whether the occurrence of nocturnal asymptomatic, serious, clinically important hypoglycemia (NSH) could be predicted based on glucose values on the previous day and the following morning of the day of onset.

Materials and Methods: This study examined patients with type 1 diabetes who underwent continuous glucose monitoring assessments and received insulin degludec. NSH was defined as glucose level < 54 mg/dL detected between 24.00 and 06.00 hours. The participants were evaluated to determine the following: (i) glucose level at bedtime (24.00 hours) on the previous day (BG); (ii) fasting glucose level (FG); and (iii) the range of post-breakfast glucose elevation. The patients were divided into those with NSH and those without, and compared using t-tests. Optimal cut-off values for relevant parameters for predicting NSH were determined using receiver operating characteristic analysis.

Results: The study included a total of 31 patients with type 1 diabetes (mean glycated hemoglobin value 7.8 ± 0.7%). NSH occurred in eight patients (26%). BG and FG were significantly lower in those with NSH than in those without (P = 0.044, P < 0.001). The range of post-breakfast glucose elevation was significantly greater in those with NSH than in those without. The cut-off glucose values for predicting NSH were as follows: BG = 90 mg/dL (sensitivity 0.83/specificity 0.75/area under the curve 0.79, P = 0.017) and FG = 69 mg/dL (0.83/0.75/0.86, P = 0.003).

Conclusions: The results showed that in patients with type 1 diabetes receiving insulin degludec, BG < 90 mg/dL and FG < 69 mg/dL had an approximately 80% probability of predicting the occurrence of NSH.

INTRODUCTION
Although it is assumed that tight glycemic control is required to prevent long-term diabetes complications in patients with type 1 diabetes1, research also suggests that these patients are associated with a significantly increased risk of mortality, even when their glycated hemoglobin (HbA1c) values are controlled at ≤ 6.9%2. A possible reason for this association is that lowering HbA1c for tight glycemic control might be associated with the onset of hypoglycemia in these patients, thereby increasing their risk for mortality3; thus, when managing patients with type 1 diabetes, it is crucial to focus on improving their HbA1c levels without causing hypoglycemia.

Because nocturnal asymptomatic hypoglycemia remains rather difficult to identify using just HbA1c or self-monitoring of blood glucose measurements, continuous glucose monitoring (CGM) is useful4. Indeed, CGM-based studies have shown that nocturnal hypoglycemia does frequently occur in patients with type 1 diabetes5,6, with the caveat that CGM is not readily
available for use in patients with type 1 diabetes because of cost and other considerations.

We reported earlier that an acute post-breakfast glucose elevation predicts the occurrence of nocturnal asymptomatic hypoglycemia (<70 mg/dL) in patients receiving insulin degludec whose fasting glucose levels are <84 mg/dL. The American Diabetes Association and European Association for the Study of Diabetes proposed the criteria for hypoglycemia for use in clinical studies as “blood glucose levels of <54 mg/dL in non-diabetes individuals which do not occur under physiological conditions” or “severe hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery” in their 2016 joint consensus statement.

It has been reported that in type 1 diabetes patients, the risk of developing severe hypoglycemia is fourfold higher if the patient is not aware of hypoglycemia defined as a blood glucose level of <54 mg/dL. In particular, it has been reported that nocturnal hypoglycemia is likely to occur because of a decrease in the compensatory secretion of adrenaline in response to hypoglycemia, and as a result, bradycardia that leads to cardiac arrest is induced. Therefore, it has been suggested that severe hypoglycemia is associated with sudden death, which is called “dead in bed syndrome”. Furthermore, severe hypoglycemia has been shown to significantly increase the risk of mortality after its onset in patients with diabetes, regardless of whether they have a prior history of cardiovascular disease. Thus, the American Diabetes Association/European Association for the Study of Diabetes emphasized preventing hypoglycemia of ≤54 mg/dL by defining it as “serious, clinically important hypoglycemia”. However, no study has determined whether glycemic variability occurring immediately before and after dinner on the previous day, and later before and after breakfast can predict the occurrence of nocturnal asymptomatic hypoglycemia, defined as blood glucose level <70 or ≤54 mg/dL.

Thus, the present study used CGM data to determine whether glycemic variability on the previous day and next morning can predict the occurrence of nocturnal asymptomatic hypoglycemia or the occurrence of severe, clinically significant nocturnal asymptomatic hypoglycemia in outpatients with type 1 diabetes receiving a multiple daily injection regimen containing insulin degludec as a long-acting soluble insulin.

METHODS

Patients

This study included outpatients with type 1 diabetes whose HbA1c value was >6.9% but <9%, and who were receiving a multiple daily injection regimen containing a rapid-acting insulin as bolus insulin and insulin degludec as a long-acting soluble insulin. All patients were allowed to inject insulin at suitable times during their day according to their lifestyle habits, with the insulin dose for each injection determined by their attending physicians. All patients were enrolled in the study after signing informed consent to study participation.

Trial design

All patients were fitted with a CGM device (iPro2; Medtronic Minimed, Northridge, CA, USA) in the outpatient clinic after ≥4 weeks of treatment with insulin degludec (Figure 1). During these assessments, they were given four standardized retort test meals from the evening of day 1 to the evening of day 2. The total calorie intake on day 1 was 591.3 kcal (carbohydrates 65.1%, proteins 15.9% and lipids 19.0%), and on day 2, it was 1,835.3 kcal (breakfast on day 2 contained 616 kcal: carbohydrates 63.6%; proteins 16.5% and lipids 19.9%).

Figure 1 | Study design. *Each patient was fitted with a continuous glucose monitoring (CGM) device in an outpatient clinic and 24 h data were collected for comparison under the same test meals. †Nocturnal asymptomatic hypoglycemia (NH) was defined as hypoglycemia (<70 mg/dL) occurring between 24.00 hours and 06.00 hours. ‡Nocturnal asymptomatic, serious hypoglycemia (NSH) was defined as serious hypoglycemia (<54 mg/dL) occurring between 24.00 hours and 06.00 hours. HbA1c, glycated hemoglobin.
CGM data obtained from 18.00 hours on day 1 to 24.00 hours on day 2 were included for analysis. Patients were excluded from the analysis if they had taken oral glucose after becoming aware of nocturnal hypoglycemia. The presence or absence of nocturnal hypoglycemia was defined as the presence or absence of nocturnal asymptomatic hypoglycemia (NH; <70 mg/dL) occurring between 24.00 hours and 06.00 hours or nocturnal asymptomatic, serious, clinically important hypoglycemia (NSH; <54 mg/dL)\(^8\).

**Primary end-points**
The following parameters were evaluated to determine glycemic variability during the previous night: (I) pre-dinner glucose levels; (II) post-dinner glucose levels (peak, 1- and 2-h postprandial values); (III) the range of post-dinner glucose elevation (from pre-dinner to peak, 1- and 2-h postprandial values); (IV) the post-dinner glucose concentration gradient (from pre-dinner to peak, 1- and 2-h postprandial values); (V) bedtime glucose levels (24.00 hours); (VI) the range from pre- or post-dinner to bedtime glucose levels (from pre-dinner, 1- and 2-h postprandial to bedtime values); and (VII) the concentration gradient from pre- or post-dinner to bedtime (from pre-dinner, 1- and 2-h postprandial to bedtime values). As in our earlier study\(^7\), the following parameters were used to determine glycemic variability before and after breakfast: (i) fasting glucose levels; (ii) post-breakfast glucose levels (peak, 1- and 2-h postprandial values); (iii) the range of post-breakfast glucose elevation (peak, 1- and 2-h postprandial values); and (iv) the post-breakfast glucose concentration gradient (peak, 1- and 2-h postprandial values).

**Statistical analysis**
The patients were divided into those with NH and those without to compare parameters I–VII and i–iv using \(t\)-tests. In summary, we determined whether NH can be predicted to occur based on parameters I–VII excluding parameters i–iv, whose potential to predict the occurrence of NH was reported previously\(^7\), and whether NSH can be predicted to occur based on parameters I–VII and i–iv; finally, when prediction was possible, the suitable cut-off values for such a prediction were determined using receiver operating characteristic analyses.

All statistical analyses were carried out using SPSS 26.0 (SPSS Inc., Chicago, IL, USA; www.spss.com/). All data are presented as the mean ± standard deviation. A \(P\)-value of < 0.05 (two-tailed) was taken to indicate statistical significance.

The present study was carried out with the approval of the institutional review board of Jikei University School of Medicine as a subanalysis of the “the Jikei-Evaluation of the basal insulin analog Tresiba (insulin degludec), a new basal insulin analog, for (nocturnal) glycemic variability as compared to an existing basal insulin analog using continuous glucose monitoring in basal–bolus treatment for type 1 diabetes – JETI Study” (UMIN000013817)\(^{12,13}\), and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

### RESULTS
CGM assessments were carried out on a total of 31 patients with type 1 diabetes who were receiving a multiple daily injection regimen, gave informed consent to participate in the study and reported not having taken glucose for hypoglycemic episodes after becoming aware of their onset. As in our earlier study\(^7\), the study participants included 14 men (45.2%) with a mean age of 46.9 ± 11.4 years (presented as the mean ± standard deviation hereafter), HbA1c level of 7.8 ± 0.7%, body mass index of 22.4 ± 3.0 kg/m\(^2\) and duration of diabetes of 19.5 ± 9.7 years (all values were previously reported in our

#### Table 1 | Comparison of patient profiles and insulin doses between patients with and without hypoglycemia

| Patient Profiles and Insulin Doses | Overall | Patients with NH | Patients without NH | **P-value** | Patients with NSH | Patients without NSH | **P-value** |
|-----------------------------------|---------|------------------|---------------------|------------|------------------|---------------------|------------|
| Patients tested (n)               | 31      | 16               | 15                  |            | 8                | 23                  |            |
| Age (years)                       | 46.9 ± 11.4 | 49.2 ± 12.5     | 44.5 ± 10.1         | \(P = 0.265\) | 47.0 ± 13.5     | 46.9 ± 10.9         | \(P = 0.986\) |
| HbA1c (%)                         | 7.8 ± 0.7  | 7.8 ± 0.7        | 7.8 ± 0.7           | \(P = 0.084\) | 7.7 ± 0.6        | 7.9 ± 0.8           | \(P = 0.471\) |
| Body mass index (kg/m\(^2\))      | 22.4 ± 3.0 | 22.5 ± 3.4       | 22.4 ± 2.5          | \(P = 0.960\) | 21.5 ± 3.0       | 22.8 ± 2.9          | \(P = 0.299\) |
| Duration of diabetes (years)      | 195.9 ± 9.7 | 239.0 ± 10.3     | 149.3 ± 6.6         | \(P = 0.000^*\) | 193.9 ± 9.5     | 192.1 ± 10.1        | \(P = 0.985\) |
| Total daily insulin dose (U/kg)   | 0.65 ± 0.20 | 0.65 ± 0.19      | 0.65 ± 0.22         | \(P = 0.035\) | 0.67 ± 0.15     | 0.64 ± 0.22         | \(P = 0.777\) |
| Basal insulin ratio (%)           | 39.1 ± 11.9 | 42.1 ± 11.6      | 35.8 ± 11.6         | \(P = 0.139\) | 40.8 ± 9.1      | 38.5 ± 12.8         | \(P = 0.646\) |
| Bolus insulin dose before dinner (U/kg) | 0.15 ± 0.06 | 0.14 ± 0.06      | 0.15 ± 0.07         | \(P = 0.069\) | 0.14 ± 0.03     | 0.15 ± 0.07         | \(P = 0.638\) |
| Bolus insulin dose before breakfast (U/kg) | 0.12 ± 0.05 | 0.11 ± 0.05      | 0.13 ± 0.06         | \(P = 0.039\) | 0.13 ± 0.06     | 0.12 ± 0.06         | \(P = 0.659\) |

Data are expressed as the mean ± standard deviation. \(^*P < 0.05\). \(^\dagger\)Unpaired Student’s two-sample \(t\)-test was used for comparisons between the patients with and without nocturnal asymptomatic hypoglycemia (NH; <70 mg/dL). \(^\ddagger\)Unpaired Student’s two-sample \(t\)-test was used for comparisons between the patients with and without nocturnal asymptomatic serious hypoglycemia (NSH; <54 mg/dL). HbA1c, glycated hemoglobin.
Patients with nocturnal asymptomatic hypoglycemia (NH; no signifi-
cance) and non-NH were found to have occurred in 16 (51.6%) and
eight (25.8%) patients, respectively. There was no significant
difference between those with NH and those without
regarding age, HbA1c, body mass index, duration of diabetes,
total insulin dose or basal–bolus insulin ratio (results for NH as
previously published); there was also no difference between the
groups regarding their bolus insulin dose before dinner and
before breakfast (Table 1). None of the patients injected extra
bolus insulin after meals. Figure 2 shows the glucose pro-
files of those with NH or NSH and those without NH or NSH from
before dinner on the previous night to post-breakfast.

Table 2 summarizes the results for the parameters measured
pre- and post-dinner on the previous day, and pre- and post-
breakfast on the day of glucose variability for those with NH or
NSH versus those without (pre-and post-breakfast results for
NH as previously published). The pre-dinner glucose levels did
not differ between NH and non-NH, or NSH and non-NSH
patients (117 ± 73 mg/dL vs 160 ± 89 mg/dL; P = 0.155, and
106 ± 72 mg/dL vs 149 ± 85 mg/dL; P = 0.216). Furthermore,
no significant difference was observed between these groups in
post-dinner peak, 1- or 2-h glucose levels. The range of post-
dinner peak glucose elevation tended to be greater in those with
NH, but was not significantly different between those with
NSH and those without. In contrast, the bedtime glucose levels
(24.00 hours) were significantly lower in those with NH than
in those without (106 ± 48 mg/dL vs 155 ± 78 mg/dL;
P = 0.045) and were significantly lower in those with NSH
than in those without (88 ± 44 mg/dL vs 144 ± 69 mg/dL;
P = 0.044). Although the range of the glucose decrease from
before dinner to bedtime was not significantly different between
the groups, the range of the glucose decrease from 1 h post-
prandial to bedtime tended to be less in those with NH than in
those without (P = 0.053), and was significantly less in those
with NSH than in those without (P = 0.047). Furthermore, the
range of the glucose decrease from 2 h postprandial to bedtime
was significantly less in those with NH than in those without
(P < 0.001). In contrast, the glucose concentration gradient
from before and after dinner to bedtime was not significantly
different between the groups.

The fasting glucose levels the next morning were significantly
lower in those with NSH (61 ± 13 mg/dL) than in those without
(130 ± 68 mg/dL; P < 0.001). The post-breakfast glucose levels
were not significantly different between the groups for the peak, 1-
and 2-h values, but the range of the glucose elevation was signifi-
cantly greater in those with NSH for the peak, 1- and 2-h values
(peak value 160 ± 66 mg/dL vs 69 ± 81 mg/dL, P = 0.008; 1-h
value 105 ± 50 mg/dL vs 54 ± 49 mg/dL, P = 0.016; and 2-h
value 145 ± 85 mg/dL vs 57 ± 80 mg/dL, P = 0.014). The post-
breakfast glucose concentration gradient was also significantly
different between the groups (peak 1.68 ± 0.63 mg/dL/min vs
0.73 ± 0.94 mg/dL/min, P = 0.013; 1-h value 1.75 ± 0.83 mg/
dL/min vs 0.90 ± 0.81 mg/dL/min, P = 0.016; and 2-h value
1.20 ± 0.71 mg/dL/min vs 0.48 ± 0.67 mg/dL/min, P = 0.014).

Figure 3 shows the number of patients who experienced NH
or NSH at each time point (NH results as previously pub-
lished), and shows that NH and NSH occurred most fre-
quently between 04.00 hours and 06.00 hours. Of note, an
analysis of the patients as stratified by timing of injection of
insulin degludec confirmed this finding.
Table 2 | Comparison of glycemic variability between patients with and without hypoglycemia

|                                | Overall (n = 31) | Patients with NH (n = 16) | Patients without NH (n = 15) | P-value† | Patients with NSH (n = 8) | Patients without NSH (n = 23) | P-value‡ |
|--------------------------------|------------------|---------------------------|-----------------------------|----------|---------------------------|-----------------------------|----------|
| Night-time (24:00–06:00 hours) |                  |                           |                             |          |                           |                             |          |
| Glucose nadir levels (mg/dL)  | 87 ± 53          | 53 ± 10                   | 124 ± 56                    | P < 0.001* | 45 ± 5                    | 102 ± 54                    | P < 0.001* |
| Duration of serious hypoglycemia, <54mg/dL (min) | 39 ± 90          | –                          | –                           |          | 150 ± 124                 | 0 ± 0                       | P < 0.001* |
| Glucose nadir levels (mg/dL)  | 80 ± 121         | 155 ± 129                 | 0 ± 0                       | P < 0.001* | –                        | –                           |          |
| Average glucose levels (mg/dL) | 115 ± 57         | 82 ± 27                   | 150 ± 60                    | P < 0.001* | 63 ± 15                   | 133 ± 55                    | P < 0.001* |
| SD of glucose levels (mg/dL)  | 18 ± 11          | 20 ± 13                   | 16 ± 7                      | P = 0.273 | 15 ± 12                   | 19 ± 10                     | P = 0.364 |
| Pre-dinner glucose levels (mg/dL) | 138 ± 83        | 117 ± 73                  | 160 ± 89                    | P = 0.155 | 106 ± 72                  | 149 ± 85                    | P = 0.216 |
| Post-dinner glucose levels (mg/dL) | 191 ± 73        | 198 ± 66                  | 184 ± 81                    | P = 0.604 | 187 ± 81                  | 192 ± 72                    | P = 0.870 |
| Postprandial 1 h               | 170 ± 69         | 167 ± 57                  | 173 ± 81                    | P = 0.794 | 166 ± 65                  | 171 ± 71                    | P = 0.866 |
| Postprandial 2 h               | 158 ± 70         | 165 ± 72                  | 151 ± 69                    | P = 0.566 | 149 ± 83                  | 161 ± 67                    | P = 0.675 |
| Range of post-dinner glucose elevation (mg/dL) | 53 ± 89          | 81 ± 73                   | 24 ± 97                     | P = 0.074 | 81 ± 73                   | 43 ± 93                     | P = 0.311 |
| Postprandial 1-h               | 32 ± 67          | 50 ± 63                   | 13 ± 68                     | P = 0.134 | 60 ± 78                   | 22 ± 62                     | P = 0.176 |
| Postprandial 2-h               | 20 ± 98          | 48 ± 99                   | −9 ± 91                     | P = 0.104 | 43 ± 106                  | 13 ± 97                     | P = 0.464 |
| Post-dinner concentration gradient (mg/dL/min) | 0.73 ± 0.88 | 0.98 ± 0.70 | 0.47 ± 0.99 | P = 0.106 | 1.09 ± 0.75 | 0.60 ± 0.90 | P = 0.183 |
| Preprandial 1-h                | 0.53 ± 1.12      | 0.83 ± 1.05               | 0.22 ± 1.14                 | P = 0.134 | 1.00 ± 1.30               | 0.37 ± 1.03                 | P = 0.176 |
| Preprandial 2-h                | 0.34 ± 1.64      | 0.80 ± 1.66               | −0.16 ± 1.52                | P = 0.104 | 0.71 ± 1.77               | 0.21 ± 1.61                 | P = 0.464 |
| Bedtime glucose levels (mg/dL) | 130 ± 68         | 106 ± 48                  | 155 ± 78                    | P = 0.045* | 88 ± 44                   | 144 ± 69                    | P = 0.044* |
| Range from pre- or post-dinner to bedtime glucose levels (mg/dL) | −8 ± 82          | −11 ± 83                  | −5 ± 83                     | P = 0.856 | −18 ± 80                  | −5 ± 83                     | P = 0.703 |
| Postprandial 1 h               | −40 ± 61         | −61 ± 60                  | −19 ± 55                    | P = 0.053 | −78 ± 55                  | −27 ± 58                    | P = 0.047* |
| Postprandial 2 h               | −29 ± 55         | −59 ± 49                  | 4 ± 41                      | P < 0.001* | −61 ± 54                  | −17 ± 47                    | P = 0.112 |
| Concentration gradient from pre- or post-dinner to bedtime (mg/dL/min) | −0.07 ± 0.07 | −0.07 ± 0.37 | −0.08 ± 0.57 | P = 0.953 | −0.10 ± 0.42 | −0.06 ± 0.50 | P = 0.815 |
| Time to bedtime from pre-dinner (min) | 229 ± 75        | 252 ± 46                  | 205 ± 93                    | P = 0.095 | 249 ± 41                  | 223 ± 83                    | P = 0.258 |
| Fasting glucose levels (mg/dL) | 112 ± 66         | 82 ± 48                   | 144 ± 69                    | P = 0.009* | 61 ± 13                   | 130 ± 68                    | P < 0.001* |
| Post-breakfast glucose levels (mg/dL) | 204 ± 60        | 214 ± 62                  | 194 ± 59                    | P = 0.358 | 221 ± 57                  | 198 ± 62                    | P = 0.364 |
| Postprandial 1 h               | 179 ± 55         | 169 ± 46                  | 190 ± 62                    | P = 0.310 | 167 ± 40                  | 184 ± 59                    | P = 0.457 |
| Postprandial 2 h               | 192 ± 65         | 195 ± 79                  | 188 ± 49                    | P = 0.752 | 206 ± 78                  | 187 ± 61                    | P = 0.485 |
| Range of post-breakfast glucose elevation (mg/dL) | 92 ± 86          | 132 ± 73                  | 50 ± 81                     | P = 0.006* | 160 ± 66                  | 69 ± 81                     | P = 0.008* |
| Postprandial 1 h               | 67 ± 53          | 87 ± 47                   | 46 ± 53                     | P = 0.028* | 105 ± 50                  | 54 ± 49                     | P = 0.016* |
| Postprandial 2 h               | 80 ± 89          | 113 ± 84                  | 44 ± 83                     | P = 0.028* | 145 ± 85                  | 57 ± 80                     | P = 0.014* |
| Post-breakfast concentration gradient (mg/dL/min) | 0.97 ± 0.96 | 1.42 ± 0.72 | 0.49 ± 0.97 | P = 0.005* | 1.68 ± 0.63 | 0.73 ± 0.94 | P = 0.013* |
| Postprandial 1 h               | 1.12 ± 0.89      | 1.45 ± 0.78               | 0.77 ± 0.88                 | P = 0.028* | 1.75 ± 0.83               | 0.90 ± 0.81                 | P = 0.016* |
| Postprandial 2 h               | 0.67 ± 0.74      | 0.94 ± 0.70               | 0.37 ± 0.69                 | P = 0.028* | 1.20 ± 0.71               | 0.48 ± 0.67                 | P = 0.014* |

Data are expressed as the mean ± standard deviation (SD). *P < 0.05. †Unpaired Student’s two-sample t-test was used for comparisons between the patients with and without nocturnal asymptomatic hypoglycemia (NH; <70 mg/dL). ‡Unpaired Student’s two-sample t-test was used for comparisons between the patients with and without nocturnal asymptomatic serious hypoglycemia (NSH; <54 mg/dL).

Receiver operating characteristic analysis was used to determine the cut-off values for the prediction of NH and NSH (Figure 4). The values for NH were bedtime glucose level = 133 mg/dL (sensitivity 0.53, specificity 0.75, area under the curve 0.71; P = 0.046), fasting glucose level = 84 mg/dL (0.80/0.75/0.80; P = 0.004), and range of post-breakfast glucose
The values for NSH were bedtime glucose level = 90 mg/dL (0.83/0.75/0.79; P = 0.017), fasting glucose level = 69 mg/dL (0.83/0.75/0.86; P = 0.003), and range of post-breakfast glucose elevation >82 mg/dL 1-h postprandial (0.75/0.61/0.74; P = 0.045) and >119 mg/dL 2-h postprandial (0.63/0.70/0.76; P = 0.032).

DISCUSSION

The present study investigated whether the occurrence of NH or NSH could be predicted in type 1 diabetes patients receiving insulin degludec based on CGM data for glycemic variability occurring immediately before and after dinner on the previous day, and later before and after breakfast. The results showed that NH and NSH could not be predicted using the glycemic variability before and after dinner on the previous day, but that it could be predicted using the bedtime glucose levels and glycemic variability before and after breakfast next morning.

Our research group reported earlier that the fasting glucose level (<84 mg/dL) and range of post-breakfast glucose elevation at 1 and 2 h post-breakfast (>69 mg/dL and >99 mg/dL, respectively) had a 60–80% chance of predicting the occurrence of NH (<70 mg/dL) in patients with type 1 diabetes receiving

**Figure 3** | Number of patients experiencing hypoglycemia at each time segment. (a) Overall for nocturnal asymptomatic hypoglycemia (NH: <70 mg/dL). (b) Overall for nocturnal asymptomatic serious hypoglycemia (NSH: <54 mg/dL). (c) Insulin degludec (IDeg) once in the evening or at bedtime (NH). (d) IDeg once in the evening or at bedtime (NSH). (e) IDeg once in the morning (NH). (f) IDeg once in the morning (NSH).
insulin degludec⁷. In this study, the receiver operating characteristic-derived cut-off values for predicting NSH (<54 mg/dL) included the fasting glucose level = 69 mg/dL and the range of the post-breakfast glucose elevation at 1 and 2 h post-breakfast 82 mg/dL and 119 mg/dL, respectively. Again, study results suggest that, even without recourse to CGM assessments, measured pre-breakfast, 1- and 2-h post-breakfast glucose levels, coupled with measured 2-h post-breakfast glucose excursions and post-breakfast glucose gradients, might have a close to 70–80% probability of estimating the occurrence of NSH. Notably, numerous CGM-based studies carried out to date, including the present study, have shown that patients with NH are associated with even lower fasting glucose levels than those without NH, with an even greater range of post-breakfast glucose elevation than those without⁵,⁷,¹⁴–¹⁸. In contrast, the results of the present study showed that patients with NSH were associated with not only lower fasting glucose levels than those with NH, but also a greater range of post-breakfast glucose elevation than those with NH. Reports have shown that insulin degludec is an ultra-long-acting soluble insulin whose action remains relatively consistent over a period of >24 h even when used once daily, thus achieving glycemic control with very little glycemic variability and few hypoglycemic episodes¹⁹–²¹. The standard deviation of night-time glucose was not significantly different between those with NH or NSH and those without (P = 0.273, P = 0.364). As shown in Figure 3, both NH and NSH tended to occur in the early morning hours between 04.00 hours and 06.00 hours. In general, the secretion of insulin counterregulatory hormones is subject to the influence of circadian rhythms, and insulin action is not completely constant due to intra-individual fluctuation. Thus, it was assumed that, between 04.00 hours and 06.00 hours, the glucose-lowering action of insulin degludec had peaked, the longest time had lapsed after dinner or the secretion of insulin counterregulatory hormones had decreased, thus accounting for the susceptibility to NH during these hours. Therefore, low fasting glucose levels might have resulted in an acute post-breakfast glucose elevation due to a post-breakfast increase in insulin counterregulatory
hormones or due to the bolus insulin dose reduced before breakfast at the patients’ own discretion.

In the present study, bedtime glucose levels were shown to be significantly lower not only in those with NH (P = 0.045), but also in those with NSH (P = 0.044), suggesting that these patients likely had a 70–80% chance of developing NH (or NSH) when their glucose levels fell below 133 mg/dL (or 90 mg/dL). Notably, a few CGM-based studies of patients with type 1 diabetes have shown that bedtime glucose levels are the most significant factor contributing to the prediction of NH, thus providing a rationale for instructing those with low bedtime glucose levels to take nutritional supplements to prevent NH. Furthermore, those with NH and NSH did not significantly differ regarding their glucose levels before and after dinner or their range of post-dinner glucose elevation or regarding the range of glucose decrease from pre-dinner to bedtime. In contrast, those with NSH were associated with a significantly lower range of glucose decrease from 1 h after dinner to bedtime than those without NSH (P = 0.047), those with NH were associated with a significantly lower range of glucose decrease from 2 h after dinner to bedtime than those without NH (P < 0.001), despite not having significantly different glucose decrease gradients, suggesting that this might partially reflect the fact that they ate dinner at different times. In the present study, a rapid-acting insulin formulation was used as a bolus insulin, and the bolus insulin dose used at dinner was not significantly different between those with NH or NSH and those without. The time to onset of action for bolus insulin ranges between 2 and 4 h, and the duration of action for bolus insulin ranges between 2 and 4 h; consequently, there was no significant difference between the groups, as the mean time from before dinner to bedtime was approximately 4 h. Furthermore, all patients were given the same test meal (total calorie intake 591.3 kcal, carbohydrates 65.1%, proteins 15.9% and lipids 19.0%)7,12–13. Thus, taken together, the significantly lower bedtime glucose levels in those with NH might have solely resulted from the glucose-lowering effect of insulin degludec rather than that of the rapid-acting insulin formulation.

Although the patients did not significantly differ regarding the times they injected insulin degludec, as previously reported, more patients with NH (without NSH) tended to have injected it once in the evening or at bedtime: six (33.3%; 12 [66.7%]) injected it once in the evening or at bedtime, and two (15.4%; 11 [84.6%]) injected it once in the morning (P = 0.26). Although insulin degludec has been shown to be longer acting than other long-acting insulin formulations and more amenable to stable absorption, thus providing a flat pattern of action, it has also been suggested that its insulin action might not always remain stable because of its intra-individual variations. Thus, when insulin degludec is injected once in the evening or at bedtime, its action is expected to peak during the night, and it is likely that night-time insulin degludec could be associated with the onset of NSH.

The present study had several limitations. First, it involved a relatively small number of patients. Second, it was carried out in an outpatient setting, and thus, the wake-up time and bedtime varied from patient to patient. Third, it is possible that the study might have failed to accurately grasp the bolus insulin dose in patients with NH. Finally, the present study included only patients receiving insulin degludec as a long-acting soluble insulin. Clinical studies with larger sample sizes and a long-acting soluble insulin other than insulin degludec should be carried out in the future. Despite these limitations, however, the study provides meaningful findings that will allow the onset of NH or NSH to be predicted in clinical practice, even without using CGM.

Our intention is that the data reported herein will find applications in clinical practice and prove helpful as reference data in formulating a treatment approach for patients with type 1 diabetes that minimizes the risk of hypoglycemia.

ACKNOWLEDGMENTS

The authors received no specific funding for this work and would give special thanks to the study participants, Rimei Nishimura and Ms Kimie Shida for her help with data management.

DISCLOSURE

Rimei Nishimura has participated in speaker’s bureau/advisory panels for Astellas, Astra Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Johnson & Johnson, Kissei, Kowa, Medtronic, Novo Nordisk, Ono, Sanofi, Taisho, Takeda and Tanabe-Mitsubishi, and served as a consultant for Abbott, Boehringer Ingelheim, Eli Lilly and Taisho. The other authors declare no conflict of interest.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977–986.
2. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014; 371: 1972–1982.
3. Lung TW, Petrie D, Herman WH, et al. Severe hypoglycemia and mortality after cardiovascular events for type 1 diabetic patients in Sweden. Diabetes Care 2014; 37: 2974–2981.
4. Klonoff DC, Buckingham B, Christiansen JS, et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96: 2968–2979.
5. Choudhary P, Davies C, Emery CJ, et al. Do high fasting glucose levels suggest nocturnal hypoglycaemia? The Somogyi effect more fiction than fact? Diabet Med 2013; 30: 914–917.
6. The Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the
13. Takahashi H, Nishimura R, Onda Y, et al. Prediction of nocturnal hypoglycaemia unawareness by fasting glucose levels or post-breakfast glucose fluctuations in patients with type 1 diabetes receiving insulin degludec: a pilot study. PloS One 2017; 12: e0177283.

14. Høi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. The prevalence and contributors. J Paediatr Child Health 2006; 42: 758–763.

15. Wentholt IM, Maran A, Masurel N, et al. Nocturnal hypoglycaemia in Type 1 diabetic patients, assessed with continuous glucose monitoring: frequency, duration and associations. Diabet Med 2007; 24: 527–532.

16. Mitsuishi S, Nishimura R, Ando K, et al. Can fasting glucose levels or post-breakfast glucose fluctuations predict the occurrence of nocturnal asymptomatic hypoglycaemia in type 1 diabetic patients receiving basal-bolus insulin therapy with long-acting insulin? PloS One 2015; 10: e0144041.

17. Gough SC, Harris S, Woo V, et al. Insulin degludec: overview of a novel ultra long-acting basal insulin. Diabetes Obes Metab 2013; 15: 301–309.

18. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultralong-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379: 1489–1497.

19. Birkeland KI, Home PD, Wendisch U, et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care 2011; 34: 661–665.

20. Perriello G, De Feo P, Torlone E, et al. The effect of asymptomatic nocturnal hypoglycaemia on glycemic control in diabetes mellitus. N Engl J Med 1988; 319: 1233–1239.

21. Wilson DM, Calhoun PM, Maahs DM, et al. Factors associated with nocturnal hypoglycaemia in at-risk adolescents and young adults with type 1 diabetes. Diabetes Technol Ther 2015; 17: 385–391.

22. Raju B, Arbelaez AM, Breckenridge SM, et al. Nocturnal hypoglycaemia in type 1 diabetes: an assessment of preventive bedtime treatments. J Clin Endocrinol Metab 2006; 91: 2087–2092.

23. Desjardins K, Brazeau AS, Strychar I, et al. Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes? Diabetes Obes Metab 2014; 16: 577–587.

24. Howey DC, Bowsher RR, Brunelle RL, et al. [Lys(B28)], Pro–(B29)]-human insulin. A rapidly absorbed analogue of human insulin. Diabetes 1994; 43: 396–402.

25. Becker RH, Frick AD, Burger F, et al. Insulin glulisine, a new rapid-acting insulin analogue, displays a rapid time-action profile in obese non-diabetic subjects. Exp Clin Endocrinol Diabetes 2005; 113: 435–443.

26. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 2012; 14: 859–864.