Prediction of lowest nocturnal blood glucose level based on self-monitoring of blood glucose in Japanese patients with type 2 diabetes

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The authors have indicated that there are no conflicts of interest regarding the content of this article.

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Abstract

Aims: Continuous glucose monitoring (CGM) is not available for all patients with type 2 diabetes (T2D) at risk of nocturnal hypoglycemia (NH). This study was performed to predict the lowest nocturnal blood glucose (LNBG) levels.

Methods: An LNBG prediction formula was developed by multivariate analysis using the data including self-monitoring of blood glucose from a formula making (FM) group of 29 insulin-treated T2D patients with CGM. The validity of the formula was assessed by nonparametric regression analysis of actual and predicted values in a formula validation group consisting of 21 other insulin-treated patients. The clinical impact on prediction was evaluated using a Parkes error grid.

Results: In the FM group with a median age of 64.0, the following formula was established: Predicted LNBG (mg/dL) = 127.4 – 0.836 × Age (y) + 0.119 × Self-monitored fasting blood glucose (mg/dL) + 0.717 × Basal insulin dose (U/day) (standard error of calibration 17.2 mg/dL). Based on the validation results, standard error of prediction was 31.0 mg/dL. All predicted values fell within zones A (no effect on clinical action) and B (little or no effect on clinical outcome) on the grid.

Conclusions: LNBG could be predicted, and may be helpful for NH prevention.

Key words:

Type 2 diabetes

Hypoglycemia

Self-monitoring of blood glucose

Continuous glucose monitoring

1. Introduction

Type 2 diabetes (T2D), which is characterized by the development of hyperglycemia due to impaired endogenous insulin secretion and insulin resistance, is a lifestyle-related disease that is increasing in incidence worldwide. For T2D patients with poor glycemic control, pharmacotherapy is a standard strategy in addition to diet and exercise therapies. However, the onset of hypoglycemia is a considerable problem in patients on medication, especially insulin and insulin secretagogues such as sulfonylurea. Hypoglycemia can be associated with cardiovascular events, dementia, coma, and death, resulting in decreased quality of life and poor prognosis.[1,2] It is particularly notable that nocturnal hypoglycemia (NH) is experienced by 41.1% of T2D patients and 57.1% of patients with severe hypoglycemia.[3] Patients and their families often fail to recognize long-lasting NH. Furthermore, NH can also cause hyperglycemia the next morning by the Somogyi effect.

Continuous glucose monitoring (CGM) and flash glucose monitoring (FCM), which provide information on each patient's profile of glycemic variability influenced by meals, exercise, and medication, are effective methods to achieve sufficient glycemic control without NH. In Japan, however, assessment of nocturnal glycemic variability with CGM or FCM is generally difficult for general physicians because monitoring is available only in approved medical institutes. Moreover, even in medical faculties capable of such monitoring, it may often be performed during a specific time frame to determine the optimal treatment and evaluate therapeutic efficacy.

In the present study, we developed a formula for predicting the lowest nocturnal blood glucose (LNBG) level using values determined by self-monitoring of blood glucose (SMBG), insulin dose, and biological information, and then evaluated its clinical usefulness.

2. Materials and Methods

2.1 Patient inclusion

Adult insulin-treated T2D patients who had been at higher risk for hypoglycemia for various reasons (large glycemic variability, experience of hypoglycemic attack, etc.) and judged to require CGM-based determination of appropriate therapy by their diabetologists in charge were retrospectively enrolled in this study. To generate a formula for prediction of LNBG levels, all 29 patients with CGM recordings that had been admitted to our hospital during the period from February 2012 to July 2013, were assigned to the formula-making (FM) group. All 21 patients with CGM recordings that had been hospitalized (18 patients) or regularly visited our hospital (3 patients) during the period from August 2013 to March 2016, were also included as the formula-validating (FV) group. In each group, data from the first CGM were adopted for analysis if the patients had undergone CGM more than once. This study was approved by the Institutional Review Board of Shinshu University School of Medicine

2.2 Predictor setting

LNBG levels were defined as the lowest blood glucose concentrations determined by CGM readings during the period between the beginning of dinner to the start of SMBG measurement before breakfast on the following day. LNBG was calculated as the mean value when CGM was continued across multiple days. With reference to the results of univariate analysis or based on clinical significance, candidate predictors for LNBG were determined, e.g., age, physical information, biochemical test data, insulin dose, and CGM recordings in the FM group.

2.3 Physical information

Age was adopted as that on the first day of CGM during hospitalization. Height and weight were measured for calculation of body mass index (BMI) within 1 week before or after CGM.

2.4 Blood testing

The following blood biochemical tests were also conducted: HbA1c, fasting C peptide reactivity (FCPR), total cholesterol (TC), HDL-cholesterol (HDL-C), triglyceride (TG), aspartate transaminase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (γ-GTP). LDL-cholesterol (LDL-C) was calculated with the Friedewald formula (TC – HDL-C – TG/5). The values of HbA1c and FCPR were obtained within 1 month before or after CGM, and the others within 1 week before or after CGM. The values of TG, AST, and ALT were log-transformed for the analysis to achieve Gaussian distribution of values.

2.5 Insulin dose

The bolus insulin dose was determined by dosage of short-acting insulin (regular insulin) or rapid-acting insulin analogs. The basal insulin dose was considered equivalent to that of long-acting insulin analogs (insulin detemir or insulin glargine) or neutral protamine Hagedorn (NPH) insulin. If premixed insulin was administered, the bolus and basal insulin doses were calculated from its mixing ratio. In this study, the influence of antidiabetic drugs except insulin was considered to be relatively low because the dosages and types of these drugs were not changed within a few days before or after CGM recordings. Moreover, blood glucose was carefully

controlled by diabetologist to avoid the development of hypoglycemia. Medications other than insulin were therefore not considered for formula creation and validation in the clinical setting.

2.6 SMBG and continuous glucose monitoring

The Medtronic MiniMed (Northridge, CA) CGMS® System Gold™ and Terumo Co. Medisafe (Tokyo, Japan) were used for CGM and SMBG, respectively. SMBG data were obtained for CGM calibration just before each meal during the whole CGM period. Each mean value was calculated based on data harvested from CGM continued for over 1 day. Both standard deviation (SD) and coefficient of variance (CV) of each CGM-related value were computed using all data obtained during the period of CGM in each patient. In this study, preprandial glucose levels were defined as glucose values just before each meal, whereas postprandial glucose levels, expressed as glucose levels after breakfast (or lunch), were set as glucose values from the beginning of breakfast (or lunch) to the start of SMBG measurement before lunch (or dinner). Nocturnal glucose levels were defined as glucose concentrations during the period between the beginning of dinner and the start of SMBG measurement before breakfast on the following day. Definitions of each CGM reading are shown schematically in Fig. 1.

2.7 Formula creation/validation and statistical analysis

Univariate analysis was performed to produce a correlation matrix between two variables. Spearman's rank correlation coefficient (ρ), *t*-value, and *p*-value of each correlation were also calculated.

Multivariate analysis of LNBG was performed using the determined candidate predictors.

Explanatory variables were selected based on the adjusted determination coefficient (R^2), standard error of correlation (SEC), multiple correlation coefficient (R), and *p*-value obtained from multivariate analysis, and then a formula for prediction of LNBG values was developed. The consistency of estimated LNBG values with the actual measured values was examined by Parkes error grid analysis, a tool to evaluate the clinical precision of SMBG instruments. In this analysis, the values obtained were plotted on a graph with the reference levels of blood glucose on the abscissa and the measured level from the subject instrument on the ordinate. Each zone was defined as follows[4,5]:

Zone A: no effect on clinical action

Zone B: altered clinical action (little or no effect on clinical outcome)

Zone C: altered clinical action (likely to affect clinical outcome)

Zone D: altered clinical action

In the FV group, the relationship between predicted and measured values was examined by regression analysis, and the formula was then validated by standard error of prediction (SEP). The clinical impact on prediction was also assessed by plotting the actual measured values and the predicted values of each group on the Parkes error grid. StatFlex ver. 6 (Artech Co., Ltd., Osaka, Japan) and JMP (SAS Institute, Cary, NC) were utilized to create and validate the prediction formula. Microsoft Excel (Microsoft Co., Redmond, WA) was used for Parkes error grid analysis.

Quantitative data were described by the median and interquartile range. The differences in each item were examined for significance by Mann–Whitney U test or Fisher's exact test. In the analysis, $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1 Clinical characteristics of patients

The median age of the patients in the FM group (17 males and 12 females) was 64 years, which was the same as that in the FV group (8 males and 13 females). The FM group showed a diabetes duration of 14.0 years, which was 4.0 years shorter than that of the FV group ($p = 0.006$). The mean BMI of the FM group and the FV group were 24.8 kg/m^2 and 25.3 kg/m^2, respectively. In both groups, the mean HbA1c was > 8%, whereas the median eGFR was 60 mL/min/1.73 m^2. The FV group showed significantly lower LDL-C level than the FM group (94.6 vs. 109.9 mg/dL, respectively, $p = 0.011$). Total insulin dose (TID) was > 20 units/day, approximately 30% – 50% of which was allocated to basal insulin dose (BID) in both groups. Basal insulin dose in the FV group was significantly higher than that in the FM group (13.0 vs. 8.0 units/day, respectively, $p = 0.021$) (Table 1). The basal bolus injection regimen using rapid/short-acting and long-acting insulin analogs was predominant. Oral hypoglycemic agents and GLP-1 receptor agonists were used along with insulin in 11 patients in the FM group and 14 patients the FV group. Metformin is widely used in Japan as a major antidiabetic drug, but the present study included only a small number of patients treated with this agent. The number of metformin users included in our study population was probably less than would be seen under actual clinical conditions (Table 2).

3.2 Univariate analysis of LNBG level

First, the simple correlations between LNBG levels and explanatory variables were examined as shown in Table 3. Age showed a significant negative correlation with LNBG ($\rho = -0.420$, $p = 0.024$). Lower LNBG was significantly associated with higher levels of HDL-C ($\rho =$

−0.403, $p = 0.033$). With regard to CGM data, LNBG was positively correlated with mean glucose during the entire CGM period ($\rho = 0.432$, $p = 0.019$), SD during the entire CGM period ($\rho = -0.400$, $p = 0.032$), CV during the entire CGM period ($\rho = -0.634$, $p < 0.001$), the mean nocturnal glucose ($\rho = 0.682$, $p < 0.001$), and CV of nocturnal glucose level ($\rho = -0.432$, $p = 0.019$). The mean fasting glucose (mean SMBG-derived fasting blood glucose) was weakly correlated with LNBG, and the relation approached clinical significance ($\rho = 0.340$, $p = 0.071$). There was a weak correlation between BID and LNBG although it was not remarkably significant ($\rho = 0.237$, $p = 0.215$).

3.3 Prediction of LNBG level using SMBG

Next, to develop an SMBG-based prediction formula, the relationships between LNBG levels and explanatory variables except CGM-related parameters were assessed by multivariate analysis. The intercept, regression coefficient β, and goodness-of-fit are shown in Table 4. In the setting of all three models (Models 1−3), blood glucose level just before dinner was excluded from the explanatory variables because $p > 0.05$ in univariate analysis. In Model 1, age, FBG, blood glucose just before lunch (BG-BL), BID, HDL-C, and TG were selected as explanatory variables. The prediction formula in this model estimated R, R^2, and SEC as 0.76 ($p = 0.004$), 0.45, and 16.1 mg/dL, respectively. Model 2 adopted all of the all explanatory variables in Model 1 excluding TG and HDL-C. In this model, R, R^2, and SEC were 0.69 ($p = 0.003$), 0.38, and 16.8 mg/dL, respectively. Model 3, adopting all explanatory variables of Model 2 excluding BG-BL levels, showed lower R (0.95, $p = 0.003$) and higher SEC (17.2 mg/dL) compared with Model 2.

Using 29 data sets of the FV group, the formula was validated by SEP corresponding to

measured LNBG levels. SEPs approximately doubled SECs in all models. SEC was lowest (16.1 mg/dL), whereas SEP was highest (45.8 mg/dL) in Model 1. In contrast, SEC was highest (17.2 mg/dL), while SEP was lowest (31.0 mg/dL) in Model 3. Therefore, the following formula created based on Model 3 was considered optimal:

Predictive LNBG (mg/dL) = 127.4 – 0.836 × Age (y) + 0.119 × Self-monitored FBG (mg/dL) + 0.717 × BID (U/day)

The 2013 version of ISO15197 requires that ≥ 99% of values measured by SMBG should be within Zone A or B on the Parkes error grid.[6] All calculated values fell within these zones in both groups. The percentages of the values located in Zone A were 89.7% in the FM group and 62.1% in the FV group (Fig. 2). These findings suggested that this formula may be reliable for LNBG prediction.

4. Discussion

The present study was performed to develop a formula for prediction of LNBG using patients' medical information even when the CGM systems were not available to prevent NH in T2D patients treated with insulin.

To evaluate the suitability of subject characteristics for creating a formula for LNBG prediction, the clinical characteristics of patients in the FM group were compared with those in two previous studies, i.e., the Japan Diabetes Complication Study (JDCS) and Japan Diabetes Outcome Intervention Trial 2 (J-DOIT2). JDCS was a large-scale clinical study enrolling Japanese T2D patients with regular visits to medical institutes specializing in diabetes care.[7] The

study population, with a mean age of 59.4 ± 7.4 years, BMI of 23.1 ± 3.0 kg/m^2, and HbA1c of 7.7% ± 1.4% was considered suitable for CGM analysis. J-DOIT2 was a clinical study of Japanese T2D patients with regular visits to family doctors belonging to local medical associations.[8] The subjects seemed to have no chance of CGM and to utilize prediction of LNBG for prevention of NH. Age, BMI, and HbA1c in the medical care support group were 56.5 ± 5.9 years, 25.9 ± 4.3 kg/m^2 and 7.4% ± 1.3%, respectively, which were comparable to those of the control group (56.5 ± 5.9 years, 26.0 ± 4.2 kg/m^2 and 7.3% ± 1.2%, respectively). The mean age in the present study was close to that in JDCS and higher than that in J-DOIT2. HbA1c in our study was increased by about 1.4% – 1.8% in comparison to those in each of these clinical trials. The prediction formula in our study was developed for patients with severe diabetes. However, it may also be applicable for patients with relatively mild diabetes who are more likely to be seen by non-diabetologists. The subjects in the FV group showed more severe dysglycemia than those in J-DOIT2. However, verification of the formula and statistical extrapolation were considered appropriate because measured LNBG levels were distributed from 40.0 to 201.8 mg/dL.

Aging was independently related to lowering LNBG level in multivariate analysis. This result was strongly supported by the observation that there have been many emergency transports of elderly patients with medication for T2D because of severe hypoglycemia.[9-11] The formula indicated that low FBG level could reduce LNBG level, leading to increased risk of hypoglycemia. This finding may be reasonable because Fang *et al*.[12] also reported a positive correlation between fasting blood glucose level and NH in elderly patients with T2D. The formula included basal insulin dose, not regular insulin/short acting insulin analogs, as a determinant of predicted LNBG. This observation suggested that usage of a sufficient basal insulin dose can reduce the risk of

developing NH. In the 4-T study, an investigation on the addition of specific insulin regimens in T2D patients with OHA therapy, the regimen involving addition of prandial insulin to basal insulin resulted in the development of less hyperglycemia than other regimens involving addition of basal insulin once daily to prandial insulin three times daily or in addiction of prandial insulin once daily to biphasic insulin twice daily.[13] Deterioration of renal function (reduced eGFR) is also known to cause hypoglycemia, especially in insulin and/or insulin secretagogue-treated patients with T2D and chronic kidney disease (CKD).[11,15] Especially, in older users of antihyperglycemic medication, the incidence rate of hypoglycemia was increased with lowering eGFR.[16] However, eGFR was not found to independently influence LNBG in this analysis. This may have been partly because NH could be avoided with careful medication and blood glucose monitoring and then LNBG was maintained at a higher level. Our study also confirmed that LNBG was negatively correlated with SD and CV of glucose during the entire CGM period. This means that NH could be associated with large glycemic variability is related to previous reports that glycemic variability indices, including SD and CV of CGM-derived glucose, could predict the episodes of NH and the rate of hypoglycemia in insulin-treated patients with T2D.[17,18] However, the glycemic variability indices could not be considered in the creation of this predictive formula because the formula was based on SMBG. In addition, viability of FBG may also be a key factor for the development of NH. In secondary analyses of the Predictable Results and Experience in Diabetes through Intensification and Control to Target (PREDICTIVE) study and Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) trial, higher day-to-day fasting glycemic variability was associated with increased risks of NH and severe hypoglycemia, respectively.[19,20] However, FBG variability could also not be considered for formula creation due to insufficient FBG data.

In the present study, the accuracy of predictive LNBG levels was quantitatively estimated by SEP and the usefulness of the formula was evaluated by Parkes error grid analysis. The formulae developed by Model 3, with small SEPs, were clinically most suitable for prediction of LNBG level. Commercially available SMBG instruments guarantee measurement accuracy of 95% or readings within ± 15 mg/dL at blood glucose level < 100 mg/dL based on ISO15197: 2013. However, Model 3 showed double the standard error, with a value of 31 mg/dL. Considering the accuracy of prediction, use of the formula to lower LNBG level by adjusting basal insulin usage and nutritional balance can increase the risk of NH if the predicted values are expected to be high. However, it would be useful to apply the formula to prevent NH by dose reduction of basal insulin and appropriate extra food intake in the case of low predicted values.

There were some limitations in this study. First, the study population consisted of a small number of patients from a single center. To enhance the practical utility, the prediction formula should be assessed in larger numbers of patients visiting medical care facilities. Second, a deficit of essential explanatory variables was indicated because SEP was still large. Indeed, both a carbohydrate- and fat-rich meal and exercise markedly affect blood glucose level, although information on nutritional intake and physical activity was not available. Antidiabetic drugs other than insulin can influence the reduction of blood glucose levels to some extent, and yet the impacts of these drugs were not included in the analysis. With regard to insulin therapy, both NPH insulin and long-acting insulin analogs were regarded as “basal insulin” in this study. However, basal insulin products differ from each other in time-action profile, and therefore may affect nocturnal blood glucose levels differently. Insulin regimen, insulin therapy duration, and previous episodes of hypoglycemia may also have some effects on the prediction of LNBG. However, this study

was conducted based on careful blood glucose control by diabetologists, and therefore we believe that the proposed formula would be reliable in our clinical setting based on the results of Parkes error grid analysis. To achieve better prediction of LNBG in various clinical settings, consideration of some influencing factors, such as nutrient intake, physical activity, antidiabetic agents including insulin (e.g., dosage, type, therapy duration), and the frequency of previous hypoglycemic episodes would be required. Third, the threshold of sensitivity for CGM systems may be low when verifying LNBG. It has been noted that the accuracy of CGM readings is not necessarily higher than SMBG values because CGM values are glucose concentrations in the interstitial fluid,[21] while it can be improved by frequency and the timing of calibrations.[22] Therefore, we minimized the reduction of accuracy by adopting SMBG-derived glucose values during times of relative glucose stability, or just before meals including breakfast, for calibration. Fourth, the subjects in this study were Japanese T2D patients with a relatively long duration of diabetes, who would generally have lower BMI and less sufficient endogenous insulin secretion than those in Western countries. Therefore, the applicability of the formula developed here may be limited to such patients. Hence, race and disease condition-based formula modification would be necessary to increase its applicability.

5. Conclusions

LNBG levels could be predicted with a standard error of 31.0 mg/dL based on age, self-monitored FBG level, and BID. The prediction formula can be expected to facilitate early and appropriate prevention of NH in T2D patients treated with insulin.

Acknowledgments

We are grateful to the patients included in the study for their participation.

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Table 1 Clinical characteristics of insulin-treated patients with type 2 diabetes

	Formula making group n = 29 (29 data sets)	Formula validation group n = 21 (29 data sets)	*p*-value
Age, years	64.0 (16.0)	64.0 (10.5)	0.731
Sex, female†	12 (41.3)	13 (44.8)	0.252
Duration of diabetes, years	14.0 (17.7)	18.0 (10.0)	0.006
Total insulin dose, U/day	26.0 (17.8)	24.0 (22.8)	0.562
Basal insulin dose, U/day	8.0 (14.0)	13.0 (97.8)	0.021*
BMI, kg/m^2	24.8 (7.0)	25.3 (8.8)	0.146
HbA1c, %	8.5 (2.6)	8.8 (2.9)	1.000
FBG, mg/dL	131.5 (39.2)	125.8 (30.3)	0.356
LNBG, mg/dL	96.5 (31.4)	106.0 (36.9)	1.000
FCPR, ng/mL	1.2 (1.1)	1.9 (3.0)	0.075
LDL-C, mg/dL	109.9 (35.6)	94.6 (35.2)	0.011*
HDL-C, mg/dL	46.0 (15.5)	39.0 (24.0)	0.777
TG, mg/dL	124.0 (92.5)	155.5 (98.0)	0.291
eGFR, mL/min/1.73 m^2	67.0 (43.0)	66.0 (27.3)	0.975
AST, U/L	23.0 (18.7)	20.0 (33.5)	0.866
ALT, U/L	28.0 (25.2)	17.0 (31.3)	0.533
γ-GTP, U/L	25.0 (47.0)	32.0 (43.8)	0.704

Values are represented as median (interquartile range) in all items except sex. *Statistically significant. †The number (percentage) is indicated. BMI: body mass index, FBG: fasting blood glucose, LNBG: lowest nocturnal blood glucose, FCPR: fasting C peptide reactivity, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase.

Table 2 Antidiabetic drugs administered to the patients

	Formula making group (n = 29)	Formula validation group (n = 21)
Insulin		
Rapid insulin or short-acting insulin analog only	5	0
Long-acting insulin analog only	0	5
Rapid insulin/short-acting insulin analog plus long-acting insulin analog	18	14
Premixed insulin (NPH: rapid-acting)	5	1
50 : 50	2	1
70 : 30	3	0
Rapid insulin/short-acting insulin analog plus premixed insulin	1	1
NPH 50 : rapid-acting 50	1	0
NPH 70 : rapid-acting 30	0	1
Antidiabetic drugs combined with insulin		
Metformin only	0	3
Metformin + sulfonylurea	1	1
Metformin + α-glucosidase inhibitor	0	1
Metformin + pioglitazone	0	1
Metformin + DPP-4 inhibitor	0	0
Metformin + GLP-1 receptor agonist	1	1
Metformin + α-glucosidase inhibitor + glinide + pioglitazone + GLP-1 receptor agonist	0	1
DPP-4 inhibitor only	3	1
DPP-4 inhibitor + α-glucosidase inhibitor	2	0
DPP-4 inhibitor + pioglitazone	0	1
GLP-1 receptor agonist only	0	2
GLP-1 receptor agonist + α-glucosidase inhibitor	0	1
α-glucosidase inhibitor only	3	1
Glinide only	1	0

NPH: neutral protamine hagedorn, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide-1.

Table 3 Univariate analysis of LNBG

Dependent variable	n	Spearman's rank correlation coefficient (ρ)	*p*-value
Age, BMI and biochemical tests			
Age	29	-0.420	0.024*
BMI	29	0.228	0.234
HbA1c	26	0.173	0.400
FCPR	25	0.126	0.550
TC	28	-0.069	0.730
LDL-C	28	-0.122	0.537
HDL-C	28	-0.403	0.033*
TG	28	0.234	0.231
eGFR	29	-0.004	0.984
AST	29	-0.274	0.151
ALT	29	0.175	0.365
γ-GTP	28	-0.130	0.510
CGM			
Mean glucose just before all meals	29	0.212	0.270
Mean glucose during the entire CGM period	29	0.432	0.019*
SD during the entire CGM period	29	-0.400	0.032*
CV during the entire CGM period	29	-0.634	<0.001*
Mean fasting glucose†	29	0.340	0.071
Mean glucose after breakfast	29	0.175	0.363
Peak glucose after breakfast	29	0.072	0.712
Mean glucose just before lunch	29	-0.051	0.792
Mean glucose after lunch	29	-0.038	0.844
Peak glucose after lunch	29	-0.210	0.275
Mean glucose just before dinner	29	0.212	0.270
Mean nocturnal glucose††	29	0.682	<0.001*
Peak nocturnal glucose††	29	0.112	0.564
SD of nocturnal glucose††	29	-0.173	0.370
CV of nocturnal glucose††	29	-0.432	0.019*
Insulin			
Ratio of basal insulin dose to total insulin dose	29	0.150	0.436
Bolus insulin dose	29	0.104	0.590
Basal insulin dose	29	0.237	0.215

*Statistically significant. †Equal to self-monitoring of blood glucose (SMBG)-based mean glucose just before breakfast. ††Each value during the period from the beginning of dinner to the start of SMBG before breakfast on the following day. LNBG: lowest nocturnal blood glucose, BMI: body mass index, FCPR: fasting C peptide reactivity, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, FBG: fasting blood glucose, SD: standard deviation, CV: coefficient of variation.

Table 4 Multivariate analysis of LNBG

	Model 1	Model 2	Model 3
Intercept	106.6	137.8	127.4
Partial regression coefficient (β)			
Age	-0.681 (p = 0.019*)	-0.767 (p = 0.006*)	-0.836 (p = 0.003*)
FBG	0.355 (p = 0.013*)	0.206 (p = 0.081)	0.119 (p = 0.247)
Glucose just before lunch	-0.305 (p = 0.032*)	-0.195 (p = 0.139)	—
BID	0.818 (p = 0.073)	0.931 (p = 0.041*)	0.717 (p = 0.099)
TG	3.796 (p = 0.378)	—	—
HDL-C	-0.009 (p = 0.975)	—	—
Fitness in Regression Analysis			
Multiple correlation coefficient (R)	0.76	0.69	0.65
p-value	0.003*	0.003*	0.003*
Adjusted R^2	0.45	0.38	0.35
SEC (mg/dL)	16.11	16.78	17.22
SEP (mg/dL)	45.84	33.77	31.02

*Statistically significant. FBG: fasting blood glucose, TG: triglyceride, HDL-D: high density lipoprotein cholesterol, BID: basal insulin dose, SEC: standard error of calibration, SEP: standard error of prediction.

Figure captions

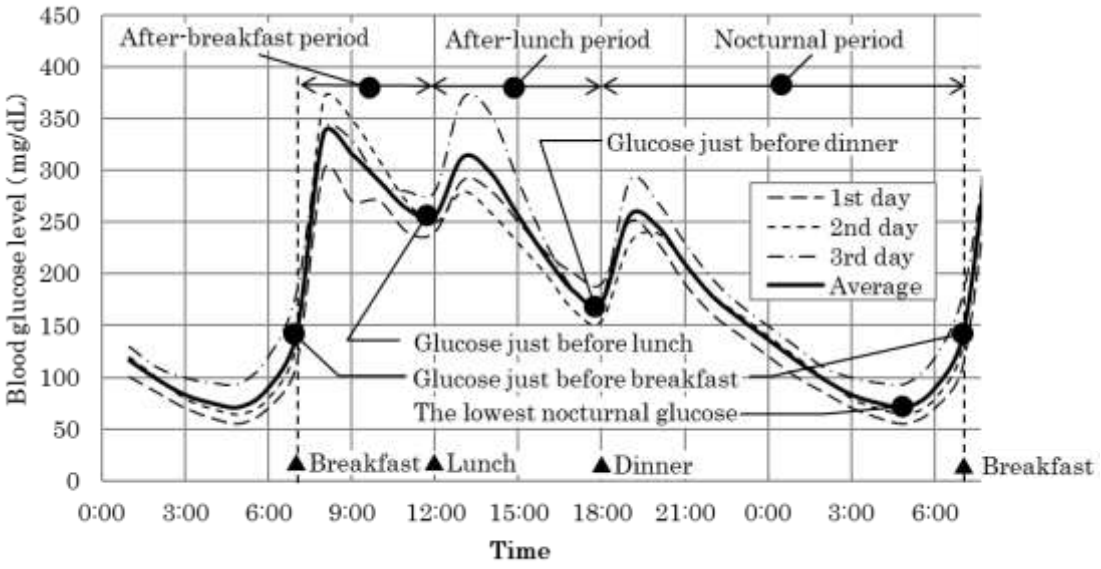

Fig. 1 Definitions of CGM data items**.** Measurement points of blood glucose and time periods are shown schematically.

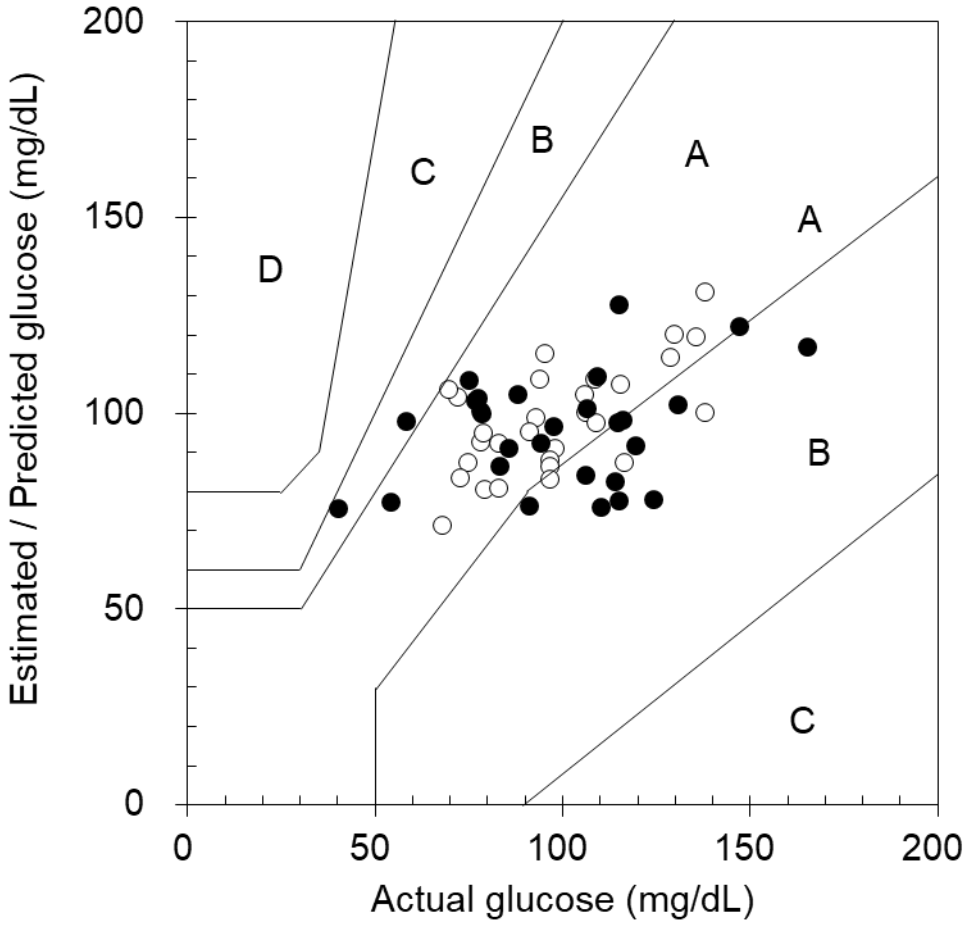

Fig. 2 Parkes error grid analysis using SMBG data. All values of estimated glucose (open circles) and predicted glucose (solid circles) were in Zone A or B.