INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Investigating the Relationship between Morning Glycemic Variability and Patient Characteristics Using Continuous Glucose Monitoring Data in Patients with Type 2 Diabetes

Soichi Takeishi, Akihiro Mori, Miyuka Kawai, Yohei Yoshida, Hiroki Hachiya, Takayuki Yumura, Shun Ito, Takashi Shibuya, Nobutoshi Fushimi, Noritsugu Ohashi and Hiromi Kawai

Abstract

Objective To investigate the relationship between patient characteristics and morning glycemic variability.

Methods We retrospectively evaluated 106 patients with type 2 diabetes who underwent continuous glucose monitoring during admission. The highest postprandial glucose level (within 3 hours after breakfast; 'highest level'), the time from the start of breakfast to the highest postprandial glucose level ('highest time'), the difference between the pre-breakfast and highest postprandial breakfast glucose level ('increase'), the area under the curve (AUC; ≥180 mg/dL) for the glycemic variability within 3 hours after breakfast ('morning AUC'), and the post-breakfast glucose gradient ('gradient') were calculated. We analyzed the associations between these factors and nocturnal hypoglycemia and the patients' characteristics by using a regression analysis.

Results After stepwise multivariate adjustment, significant independent associations were found between 'highest level' and high age, low BMI, and high HbA1c; 'highest time' and high HbA1c, low C-peptide immunoreactivity (CPR), and low fasting plasma glucose (FPG); the 'increase' and high age, low BMI, high HbA1c, low FPG and hypoglycemia; 'morning AUC' and high age, high HbA1c and hypoglycemia; and 'gradient' and long duration of diabetes and low BMI.

Conclusion Higher age and lower BMI are associated with higher 'highest' and 'increase' levels. Higher HbA1c levels were linked to a longer 'highest time', and longer durations of the diabetes, while lower BMI values were related to a higher 'gradient'.

Key words: morning glycemic variability, patient characteristics, Continuous Glucose Monitoring (CGM)

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Introduction

The post-breakfast glucose levels are often increased to a greater extent than post-lunch or post-supper glucose levels, and may cause increased glycemic variability over 24 hours (1). The glucose level after the first meal (breakfast) (2), and sometimes the Somogyi phenomenon (3) and the dawn phenomenon (4) are the main causes of increased morning glucose levels. In the case of the Somogyi phenomenon, the cause is nocturnal hypoglycemia. Thus, (i) adjusting treatment to avoid nocturnal hypoglycemia when nocturnal hypoglycemia causes increased morning glucose levels and (ii) decreasing the post-breakfast glucose levels directly by adjusting treatment, are necessary in order to improve increased post-breakfast glucose levels.

Large clinical studies have shown that hypoglycemia is strongly associated with mortality in diabetes mellitus patients (5-7). It has been suggested that nocturnal hypoglycemia is associated with not only major hyperglycemia during the daytime (8, 9), but also increased morning glucose levels (10). We have reported the relationship of major in-

Department of Endocrinology and Diabetes, Ichinomiyanishi Hospital, Japan
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Correspondence to Dr. Soichi Takeishi, souichi19811225@yahoo.co.jp

creases between the pre- and post-breakfast glucose levels and nocturnal hypoglycemia in patients with type 2 diabetes (11). We can reduce increases between the pre- and post-breakfast glucose levels and improve the increased glycemic variability over 24 hours by adjusting a patient's treatment to avoid nocturnal hypoglycemia.

Knowledge of a patient's morning glycemic variability status is important for improving increased glycemic variability over 24 hours. The measurement of pre- and post-breakfast blood glucose levels is often complicated for patients who do not use injections. Thus, it is desirable to predict morning glycemic variability using an easier method. We focused on using patient characteristics to predict morning glycemic variability (12). We investigated the relationship between patient characteristics and morning glycemic variability in type 2 diabetes patients using continuous glucose monitoring (CGM) data.

Materials and Methods

Study design and patient selection

We retrospectively analyzed 106 type 2 diabetes patients who underwent CGM during admission over a 2-year period from 2013 to 2015. A CGM (Medtronic ipro2; Medtronic MiniMed, Northridge, USA) device was attached to each patient for 4 days, and we evaluated the CGM data measured on the third day. The patients were given 3 meals per day, each with 1,440 kcal, 1,600 kcal, or 1,840 kcal (determined according to their physique) (13). Identical test meals were given to each patient based on the recommendation of the Japan Diabetes Society (carbohydrates, 60%; proteins, 18%; and lipids, 22%) (breakfast, 30%; lunch, 35%; supper, 35%), irrespective of differences in their physique. The inclusion criteria were: 1) patients who were from 20 to 90 years of age, 2) patients who took the whole quantity of every meal while undergoing CGM. The exclusion criteria were: 1) patients who were aware of their hypoglycemia and who took glucose tablets, 2) patients who had been taking α-glucosidase inhibitors (because α-glucosidase inhibitors affect the glucose gradient). Nocturnal hypoglycemia was defined as a blood glucose level of <70 mg/dL occurring from 0 AM to 8 AM.

The present study was approved by the institutional review board of Ichinomiyanishi Hospital, Japan. All of the extracted patient data were anonymized.

The outcomes and statistical analyses

The parameters used as the indices of morning glycemic variability included the highest postprandial glucose level within 3 hours after breakfast ('highest level'), the time from the start of breakfast to the highest postprandial glucose level ('highest time'), the difference between pre-breakfast and the highest postprandial breakfast glucose level ('increase'), the area under the glucose curve (≥180 mg/dL) within 3 hours after breakfast ('morning AUC'), and the post-breakfast glucose gradient ('increase'/'highest time') ('gradient') (11, 13). We analyzed the association between these indices of glycemic variability (response variable) and nocturnal hypoglycemia and the patient characteristics [age, sex, duration of diabetes, body mass index (BMI), glycosylated hemoglobin (HbA1c) concentration, C-peptide immunoreactivity (CPR), fasting plasma glucose (FPG), the C-peptide index (= fasting C-peptide immunoreactivity/FPG ×100] (CPI) and the presence of antidiabetic agents) (explanatory variable) using univariate and stepwise (method of increasing and decreasing the variables) multivariate regression analyses.

p values of <0.05 were considered to indicate statistical significance. The data are shown as the mean and standard deviation (SD). The data were analyzed using the BellCurve for Excel software program (Social Survey Research Information, Japan).

Results

Patient characteristics

Figure shows the glycemic variability over 24 hours of CGM in all of the patients. Table 1 shows the patients' characteristics. The study included 56 men and 50 women. The baseline characteristics were as follows: mean age, 66.6±11.0 years; BMI, 23.7±3.9 kg/m^2; HbA1c level, 8.7±1.4% (71.2±15.6 mmol/moL); duration of diabetes, 14.7±10.7 years; CPR, 1.4±1.0 ng/mL; FPG, 144.6±64.9 mg/dL; and CPI, 1.0±0.8. The indices of morning glycemic variability were as follows: pre-breakfast glucose level [7:00], 128.7±33.8 mg/dL; 'highest level', 226.4±62.7 mg/dL; 'highest time', 100.8±42.2 minutes; 'increase', 97.7±56.3 mg/dL; 'morning AUC', 7,027.4±9,268.6 mg·min/dL; and 'gradient', 1.1±1.2 mg/dL·min. Twenty-eight patients (26.4%) had hypoglycemia.

Primary outcomes

According to a univariate analysis, high age, long duration of diabetes, low BMI, high HbA1c, low CPR and hypoglycemia were significantly associated with the 'highest level' (ß=0.38, p=<0.0001; ß=0.36, p=0.0002; ß=-0.36, p=0.0001; ß=0.25, p=0.008; ß=-0.21, p=0.03; ß=0.25, p=0.01, respectively). High HbA1c, low CPR, low FPG, low CPI and hypoglycemia were significantly associated with the 'highest time' (ß=0.2, p=0.045; ß=0.22, p=0.02; ß=-0.47, p<0.0001; ß=-0.25, p=0.009; ß=-0.38, p<0.0001; ß=0.19, p=0.046, respectively). High age, long duration of diabetes, low BMI, high HbA1c, low CPR, low FPG and hypoglycemia were significantly associated with the 'increase' (ß=0.39, p=<0.0001; ß=0.38, p=<0.0001; ß=-0.39; p=<0.0001; ß=0.25, p=0.009; ß=-0.24, p=0.01; ß=-0.29, p=0.003; ß=0.41, p=<0.0001, respectively). High age, long duration of diabetes, high HbA1c and hypoglycemia were significantly associated with 'morning AUC' (ß=0.33, p=0.0005; ß=0.27, p=0.005; ß=0.28, p=0.003; ß=0.27, p=0.004, respectively).

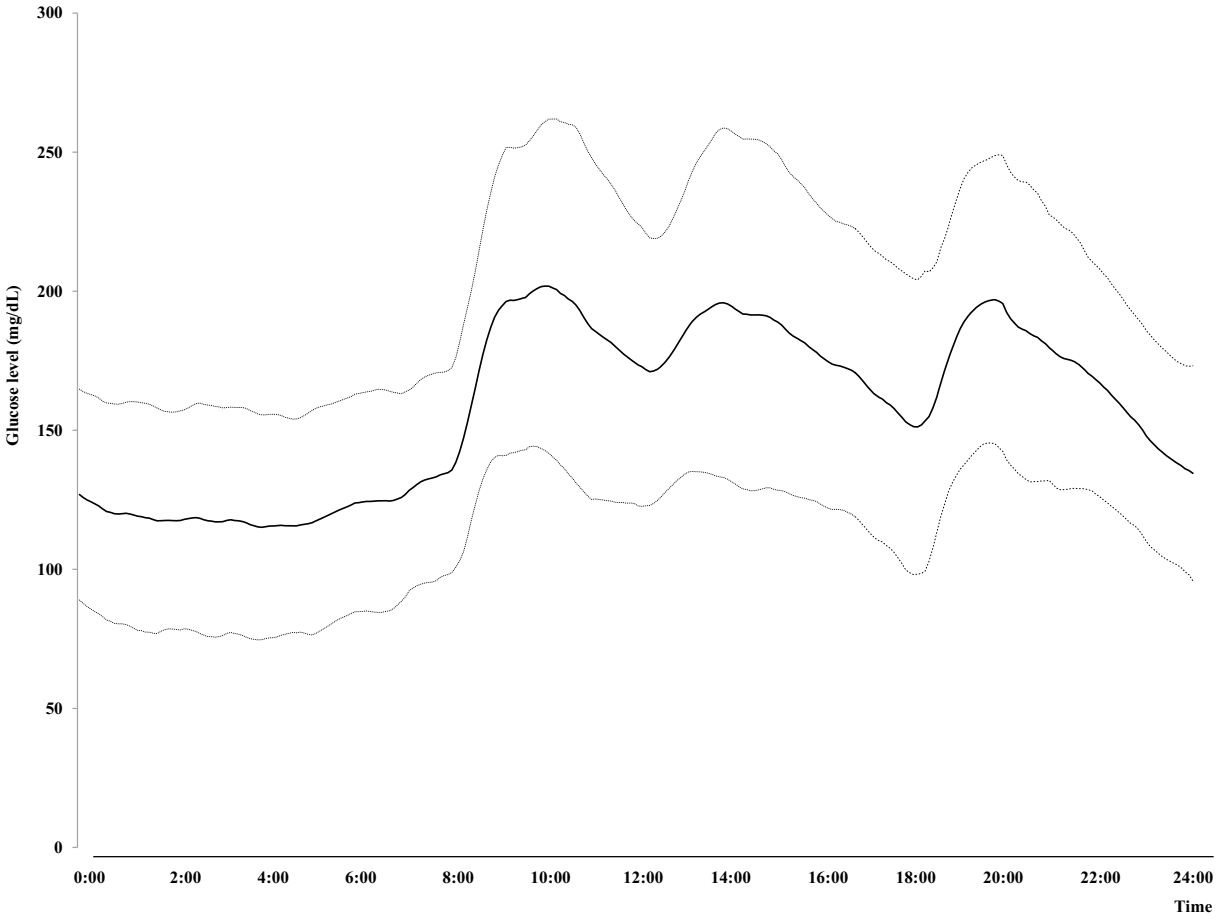

Figure. **The graph shows the glucose variability over 24 hours during continuous glucose monitoring in all of the patients. The data are shown as the mean (thick lines) and standard deviation (thin lines).**

Long duration of diabetes and low BMI were significantly associated with the 'gradient' (ß=0.3, p=0.002; ß=-0.34, p=0.0003, respectively). The use of antidiabetic agents was not associated with the indices of morning glycemic variability (Table 2).

After stepwise multivariate adjustment, high age, low BMI, and high HbA1c were significantly and independently associated with the 'highest level' (ß=0.29, p=0.002; ß=-0.26, p=0.004; ß=0.26, p=0.003, respectively). High HbA1c, low CPR, and low FPG were significantly and independently associated with the 'highest time' (ß=0.21, p=0.03; ß=-0.34, p=0.0009; ß=-0.23, p=0.02, respectively). High age, low BMI, high HbA1c, low FPG and hypoglycemia were significantly and independently associated with the 'increase' (ß=0.23, p=0.009; ß=-0.23, p=0.01; ß=0.36, p<0.0001; ß=-0.28, p=0.003; ß=0.2, p=0.01, respectively). High age, high HbA1c and hypoglycemia were significantly and independently associated with 'morning AUC' (ß=0.33, p=0.0003; ß=0.29, p=0.002; ß=0.2, p=0.03, respectively). Long duration of diabetes and low BMI were significantly and independently associated with the 'gradient' (ß=0.21, p=0.03; ß=-0.28, p=0.005, respectively) (Table 3).

The relationship between the highest postprandial glucose level within 3 hours ('the highest') and the patient characteristics

According to a univariate analysis, high age, long duration of diabetes, low BMI, high HbA1c, low CPR, low FPG, low CPI and hypoglycemia were significantly associated with the 'the highest' after lunch (ß=0.34, p=0.0004; ß=0.41, p=<0.0001; ß=-0.23, p=0.02; ß=0.27, p=0.005; ß=-0.37, p=0.0001; ß=-0.32, p=0.001, ß=-0.32, p=0.0007, ß=0.24, p=0.01, respectively). High age, long duration of diabetes, low BMI, low CPR and low FPG were significantly associated with the 'the highest' after supper (ß=0.28, p=0.004; ß=0.40, p=<0.0001; ß=-0.20, p=0.04; ß=-0.22, p=0.02; ß=-0.27, p=0.005, respectively) (Table 4).

After stepwise multivariate adjustment, high age, high HbA1c low FPG and low CPI were significantly and independently associated with 'the highest' after lunch (ß=0.20, p=0.03; ß=0.28, p=0.003; ß=-0.35, p=0.0003, ß=-0.24, p=0.008, respectively). A long duration of diabetes was significantly and independently associated with 'the highest' after supper (ß=0.35, p=0.0003) (Table 5).

Table 1. The Baseline Characteristics.

Characteristics	
N (Male / Female)	106 (56 / 50)
Age, years	66.6 ± 11.0
Duration of diabetes, years	14.7 ± 10.7
BMI, kg/m^2	23.7 ± 3.9
HbA1c (NGSP), %	8.7 ± 1.4
HbA1c (IFCC), mmol/moL	71.2 ± 15.6
CPR, ng/mL	1.4 ± 1.0
FPG, mg/dL	144.6 ± 64.9
CPI	1.0 ± 0.8
Pre-breakfast glucose level, mg/dL	128.7 ± 33.8
Highest glucose level, mg/dL	226.4 ± 62.7
Highest glucose time, minutes	100.8 ± 42.2
Increase glucose level, mg/dL	97.7 ± 56.3
AUC (≥180 mg/dL), mg·min/dL	7,027.4 ± 9,268.6
Glucose gradient, mg/dL·min	1.1 ± 1.2
Highest during 24 hours, n	
Post-breakfast	46
Post-lunch	24
Post-supper	34
Hypoglycemia, n (%)	28 (26.4)
Sulfonylurea agent, n (%)	10 (9.4)
Metformin, n (%)	68 (64.2)
Thiazolidinediones, n (%)	17 (16.0)
α- glucosidase inhibitor, n (%)	0 (0)
Insulin, n (%)	70 (66.0)
DPP-4 inhibitors, n (%)	58 (54.7)
GLP-1 receptor agonists, n (%)	13 (12.3)
Rapid-acting insulin secretagogue, n (%)	11 (10.4)
SGLT 2 inhibitor, n (%)	19 (17.9)

The data are shown as the mean and standard deviation (SD).

BMI: body mass index, HbA$_1$c: glycosylated hemoglobin, CPR: C-peptide immunoreactivity, FPG: fasting plasma glucose, CPI: C-peptide index, Highest glucose level: highest postprandial glucose level within 3 hours after breakfast, Highest glucose time: time from start of breakfast to the highest postprandial glucose level, Increase glucose level: difference between pre-breakfast and highest postprandial breakfast glucose levels, AUC (≥180 mg/dL): area under the glucose curve (≥180 mg/dL) within 3 hours after breakfast, Glucose gradient: post-breakfast glucose gradient, Highest during 24 hours: highest glucose levels during 24 hours Hypoglycemia, nocturnal hypoglycemia (<70 mg/dL from 0:00 to 8:00), DPP: dipeptidyl-peptidase, GLP: glucagon-like peptide, SGLT: Sodium glucose co-transporter

Discussion

Overall, the results of our study suggest that: Higher age and lower BMI are associated with higher 'highest' and 'increase levels'. Higher HbA1c levels are linked to longer 'highest time', and longer durations of diabetes and lower BMI are related to higher 'gradient'.

Regarding the observation that higher age is associated with a higher 'increase', it has been suggested that elderly patients with diabetes characteristically have lower pre-breakfast glucose levels, but higher post-breakfast glucose levels (14). The results of our study are in agreement with previous reports (14). Regarding the observation that a lower BMI was associated with a higher 'increase', we believe the reason for this is that patients can be diagnosed with diabetes despite having a low BMI; the insulin sensitivity of such patients increases, while their endogenous insulin secretion decreases. We therefore believe that the post-breakfast glucose levels can easily increase. Regarding the association between a higher 'gradient' and a longer duration of diabetes and lower BMI, the longer duration of diabetes and lower BMI generally leads to a decrease in endogenous insulin secretion. Decreasing endogenous insulin secretion mainly causes a higher 'gradient'. Based on the aforementioned observations, we believe that treatments that decrease the post-breakfast glucose levels in elderly diabetes patients as well as delay or reduce the increase in the post-breakfast glucose levels of diabetes patients with low BMI values should be considered.

The observation that higher HbA1c levels correspond with a longer 'highest time', that lower HbA1c levels are related to an earlier 'highest time' in patients with diabetes, and that the 'highest time' occurs early in the oral glucose tolerance test of early impaired glucose tolerance can possibly be explained by a decrease in early endogenous insulin secretion and a later recovery in endogenous insulin secretion. Thus, the 'highest time' occurs earlier. In addition, higher HbA1c is associated with a greater decrease in not only early but also late endogenous insulin secretion (15). As a result, the 'highest time' occurs later. Thus, we should also consider treatments that decrease the 'highest levels' in the later time zones from 1 hour to 2 hours after breakfast to decrease the post-breakfast glucose levels in patients with high HbA1c levels.

In the present study, the post-supper or post-lunch glucose levels may have been the highest over 24 hours because the study subjects took various medications. Thus, we also studied the relationships between the highest glucose levels and the clinical characteristics at post-supper and post-lunch. As a result, the post-lunch glucose level was associated with the patients' clinical characteristics (to the same extent as the post-breakfast glucose level), but the relationship between the post-supper glucose level and the clinical characteristics was not stronger than that observed with the post-breakfast glucose level. In this study, the number of patients who had their highest glucose levels (over a 24-hour period) at the post-breakfast measurement was greater than the number of patients whose highest glucose levels were recorded in the post-lunch measurement (46 vs. 24). We were therefore of the opinion that the present study, which aimed to predict glycemic variability based on the clinical characteristics, should focus on the post-breakfast glucose levels.

Our study results were evaluated using CGM data, which is the most useful method for evaluating glycemic variability in detail (16, 17). Our results suggested that we could predict morning glycemic variability before and after breakfast based on patient characteristics and without the use of frequent blood collection (including the self-measurement of

Table 2. **The Relationship between Morning Glycemic Variability and the Patient Characteristics.**

Univariate	Highest glucose level			Highest glucose time			Increase glucose level			AUC (≥180 mg/dL)			Glucose gradient		
Variable	a	ß	p	a	ß	p	a	ß	p	a	ß	p	a	ß	p
Age, years	83.87	0.38	<0.0001	51.15	0.2	0.045	-35.88	0.39	<0.0001	-11,547.79	0.33	0.0005	-0.24	0.19	0.06
Male sex, n	227.44	-0.02	0.88	107.18	-0.14	0.14	101.90	-0.07	0.47	7,630.21	-0.06	0.53	1.05	0.08	0.43
Duration of diabetes, years	195.55	0.36	0.0002	92.88	0.14	0.16	68.31	0.38	<0.0001	3,566.07	0.27	0.005	0.63	0.3	0.002
BMI, kg/m^2	362.13	-0.36	0.0001	111.89	-0.04	0.66	230.79	-0.39	<0.0001	15,518.35	-0.15	0.12	3.71	-0.34	0.0003
HbA1c (NGSP), %	129.52	0.25	0.008	43.98	0.22	0.02	11.58	0.25	0.009	-8,844.09	0.28	0.003	0.76	0.05	0.6
CPR, ng/mL	243.75	-0.21	0.03	126.37	-0.47	<0.0001	115.39	-0.24	0.01	8,977.63	-0.16	0.09	1.07	0.05	0.6
FPG, mg/dL	248.50	-0.16	0.11	124.60	-0.25	0.009	134.20	-0.29	0.003	6,831.99	0.009	0.92	1.50	-0.13	0.2
CPI	238.89	-0.16	0.11	121.18	-0.38	<0.0001	106.09	-0.12	0.23	9,178.57	-0.18	0.06	0.94	0.14	0.17
Hypoglycemia, n	217.21	0.25	0.01	95.96	0.19	0.046	83.85	0.41	<0.0001	5,510.05	0.27	0.004	1.10	0.06	0.52
Sulfonylurea agent, n (%)	225.92	0.02	0.8	102.46	-0.12	0.22	97.08	0.03	0.73	6,962.32	0.02	0.82	1.17	-0.04	0.66
Metformin, n (%)	228.92	-0.03	0.76	97.66	0.06	0.56	94.50	0.04	0.66	7,735.95	-0.06	0.56	1.05	0.06	0.54
Thiazolidinediones, n (%)	224.69	0.06	0.52	99.02	0.1	0.31	98.95	-0.05	0.6	6,654.22	0.09	0.35	1.19	-0.07	0.48
Insulin, n (%)	226.89	-0.01	0.96	95.81	0.09	0.38	96.43	0.02	0.87	6,406.27	0.05	0.62	1.10	0.03	0.79
DPP-4 inhibitors, n (%)	219.40	0.1	0.3	103.56	-0.06	0.55	91.48	0.1	0.3	5,603.08	0.14	0.15	1.20	-0.04	0.7
GLP-1 receptor agonists, n (%)	226.09	0.01	0.88	102.15	-0.08	0.39	96.48	0.06	0.56	7,071.91	-0.01	0.9	1.17	-0.04	0.72
Rapid-acting insulin secretagogue, n (%)	225.43	0.05	0.63	98.74	0.15	0.13	95.56	0.11	0.25	6,779.17	0.08	0.42	1.16	-0.03	0.76
SGLT 2 inhibitor, n (%)	222.89	0.12	0.22	99.16	0.09	0.38	95.95	0.07	0.5	6,428.94	0.14	0.16	1.17	-0.04	0.69

The data were subjected to a univariate regression analysis.

a: constant term, ß: standardized partial regression coefficient

Table 3. The Relationship between Morning Glycemic Variability and the Factors That were Significantly Associated with Morning Glycemic Variability (adjusted).

	Highest glucose level		Highest glucose time		Increase glucose level		AUC (≥180 mg/dL)		Glucose gradient	
Variable	ß	p	ß	p	ß	p	ß	p	ß	p
Age, years	0.27	0.004			0.17	0.046	0.3	0.0009		
Duration of diabetes, years									0.21	0.03
BMI, kg/m^2	-0.25	0.007			-0.19	0.02			-0.28	0.005
HbA1c (NGSP), %	0.25	0.005	0.20	0.04	0.33	<0.0001	0.26	0.003		
FPG, mg/dL			-0.38	<0.0001	-0.33	0.0007				
CPI			-0.33	0.0004						
Hypoglycemia, n	0.14	0.11			0.2	0.01	0.2	0.03		
a	120.36		100.86		24.03		-25,722.45		2.83	
R^2	0.26		0.26		0.42		0.21		0.14	
Significance		<0.0001		<0.0001		<0.0001		<0.0001		0.0001

The data were subjected to a stepwise multivariate regression analysis. If explanatory variables displayed multicollinearity, either one was eliminated.

Table 4. The Relationship between the Highest Postprandial Glucose Level within 3 Hours ('the Highest') and the Patient Characteristics.

Highest glucose level				Lunch			Supper
Variable	a	ß	p	a	ß	p	
Age, years	85.11	0.34	0.0004	115.24	0.28	0.004	
Male sex, n	227.16	-0.12	0.21	230.23	-0.17	0.09	
Duration of diabetes, years	182.20	0.41	<0.0001	185.53	0.40	<0.0001	
BMI, kg/m^2	309.88	-0.23	0.02	292.20	-0.20	0.04	
HbA1c (NGSP), %	110.92	0.27	0.005	152.64	0.18	0.07	
CPR, ng/mL	249.88	-0.37	0.0001	237.36	-0.22	0.02	
FPG, mg/dL	262.19	-0.32	0.001	254.78	-0.27	0.005	
CPI	245.91	-0.32	0.0007	233.14	-0.17	0.08	
Hypoglycemia, n	209.25	0.24	0.01	215.20	0.12	0.23	
Sulfonylurea agent, n (%)	220.59	-0.08	0.40	220.84	-0.06	0.52	
Metformin, n (%)	221.05	-0.03	0.79	219.97	-0.01	0.96	
Thiazolidinediones, n (%)	217.97	0.03	0.76	220.45	-0.03	0.74	
Insulin, n (%)	216.16	0.03	0.77	220.04	-0.01	0.96	
DPP-4 inhibitors, n (%)	213.23	0.08	0.42	217.26	0.03	0.73	
GLP-1 receptor agonists, n (%)	220.36	-0.06	0.53	221.03	-0.06	0.52	
Rapid-acting insulin secretagogue, n (%)	217.10	0.08	0.43	217.05	0.12	0.22	
SGLT 2 inhibitor, n (%)	215.60	0.11	0.28	221.20	-0.06	0.57	

The data were subjected to a univariate regression analysis.

Table 5. The Relationship between 'the Highest' and the Factors That were Significantly Associated with 'the Highest' (adjusted).

Highest glucose level		Lunch		Supper
Variable	ß	p	ß	p
Age, years	0.20	0.03		
Duration of diabetes, years			0.35	0.0003
HbA1c (NGSP), %	0.28	0.003		
FPG, mg/dL	-0.35	0.0003	-0.16	0.08
CPI	-0.24	0.008		
a	95.58		211.07	
R^2	0.31		0.17	
Significance		<0.0001		<0.0001

The data were subjected to a stepwise multivariate regression analysis. If explanatory variables displayed multicollinearity, either one was eliminated.

blood glucose). This information may help to provide appropriate guidance and in the selection of medications. Thus, the clinical significance of the present study is high. However, it should be noted that this study was retrospective in nature and that patients took various medications during the study period, including metformin, insulin, and insulin secreting anti-diabetic drugs. Moreover, factors that are needed to show homeostasis model assessment of insulin resistance (HOMA-R) or other factors showing insulin resistance were not measured in the subjects of the present study. Thus, the validity of these results must be confirmed in a prospective study in which antidiabetic agents are not used.

The authors state that they have no Conflict of Interest (COI).

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S.T. designed the study, collected the data, analyzed the data, and wrote the manuscript. A.M. reviewed the manuscript and revised it critically for important intellectual content. M.K., Y.Y., H.H., T.Y., S.I., T.S., N.F., N.O., and H.K. contributed to the review of the manuscript. S.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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