Glycemic Profiling in Patients with Drug-Naïve Type 2 Diabetes by Continuous Glucose Monitoring

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Abstract: The purpose of this study was to determine the glycemic profiles of drug-naïve type 2 diabetes patients according to hemoglobin A1c (HbA1c) level using continuous glucose monitoring. We aimed to clarify factors associated with HbA1c and average blood glucose level. Patients were divided into three groups according to their HbA1c level (<7.0% n=23, 7.0%≤HbA1c<8.0% n=17 and ≥8.0% n=31), and the factors associated with HbA1c and average glucose of each group were evaluated. Pre-meal glucose levels were the highest before lunch, and the 2 hour postprandial blood glucose level was the lowest after lunch. The pre-meal and postprandial blood glucose levels increased after each meal with increases in HbA1c. Average glucose level was the most significant determinant of HbA1c, whereas pre-meal glucose level at dinner was the most significant determinant of average glucose level, and the range of increase in glucose from pre-meal at dinner was the most significant determinant of standard deviation (SD) of 24 hour glucose levels. HbA1c subgroup analysis indicated that pre-meal glucose level at lunch significantly correlated with average glucose level in the HbA1c <8.0% group, while pre-meal glucose level at dinner significantly correlated with average glucose level in the HbA1c ≥8.0% group. The range of increase in glucose from pre-meal in the morning significantly correlated with SD of 24 hour glucose levels in the HbA1c <8.0% group, and the postprandial peak glucose level at lunch significantly correlated with SD of 24 hour glucose levels in the HbA1c ≥8.0% group. The results suggest that improvement of the average glucose level is necessary to improve the HbA1c levels. For patients with HbA1c <7.0%, it is important to improve blood glucose level after breakfast and before lunch to decrease the average glucose level. For patients with 7.0%≤HbA1c<8.0%, it is important to improve blood glucose level before lunch and after dinner to decrease the average glucose level. For patients with HbA1c ≥8.0%, it is important to improve blood glucose levels after lunch and before dinner to decrease the average glucose level.

Keywords: continuous glucose monitoring, drug naïve, type 2 diabetes.

(Received June 18, 2018, accepted November 2, 2018)

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**Introduction**

Blood glucose profiles differ greatly among patients with type 2 diabetes mellitus (T2DM) based on the diversity in age and lifestyles. Blood glucose profile is useful in the overall assessment of the condition and plans for treatment. The continuous glucose monitoring (CGM) system allows the monitoring of glycemic parameters by examining several variables that cannot be recorded continuously by conventional methods, such as nocturnal hypoglycemia, asymptomatic hypoglycemia, and glycemic variability, thereby providing a better picture of blood glucose status. At present, self-measurement of blood glucose (SMBG) is being used in daily clinical practice, but it is not yet widely available, at least not in Japan. A high correlation between SMBG level and hemoglobin A1c (HbA1c) level has been reported in a diabetes control and complications trial (DCCT) \[1\], and a structured testing program (STeP) study reported that treatment based on systematic measurement of blood glucose improved HbA1c levels and quality of life (QOL) without increasing the frequency of blood glucose measurements \[2\].

We reported previously that glycemic variability correlates with vascular endothelial function, which plays an important role in the development and progression of arterial sclerosis \[3\]. Although HbA1c is suitable for the assessment of chronic hyperglycemia, it does not accurately assess postprandial blood glucose and glycemic variability. Monitoring blood glucose over a period of time provides more important clinical information. Previous studies examined 24 hour glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed, drug-naïve, T2DM patients by using CGM \[4, 5\]. The results showed variability in postprandial glucose excursions in T2DM patients and that such variability correlated with HbA1c levels.

The aim of the present study was to conduct a detailed analysis of glycemic profile after each of the three daily meals in drug-naïve T2DM Japanese patients using the CGM, and to examine factors associated with HbA1c, mean blood glucose level and standard deviation (SD) of 24 hour glucose levels. Specifically, 71 such patients who used CGM were evaluated. After dividing them into three groups according to HbA1c level, we compared the glucose profiles before and after breakfast, lunch and dinner in the three groups.

**Materials and Methods**

This retrospective study evaluated drug-naïve T2DM patients admitted to our hospital and affiliated hospitals between April 2010 and April 2015. These patients were treated with diet and exercise alone and underwent CGM (CGMS\textsuperscript{®} System Gold\textsuperscript{TM}; Medtronic Inc., Fridley, MN, USA or iPro\textsuperscript{TM} 2; Medtronic, Northridge, CA, USA) until the fifth day of admission. While the study included all diabetic patients irrespective of their age or sex, we excluded those with type 1 diabetes, pancreatic diabetes, steroid diabetes, infectious disease, ketoacidosis, hyperosmolar non-ketotic coma, dialysis, or anemia, and those taking iron or erythropoietin. The study protocol was approved by the ethics review committee of the University of Occupational and Environmental Health and adhered to the revised 2000 declaration of Helsinki. Each patient volunteered to participate in the study and signed an informed consent at enrollment.

**Study design**

Patients underwent CGM for three days until the fifth day of admission. 24 hour CGM data obtained on the second or third day of recording that were stable and without missing components were used in the analysis. During hospitalization, each patient received a diet containing 25–30 kcal/kg ideal body weight (carbohydrates comprising 50–60% of the total energy intake, protein 1.0–1.2 g/kg of the ideal body weight and fat ≤ 25% of the total energy intake), according to the dietary recommendations established by the Japan Diabetes Society. Patients also performed exercises that corresponded to activities of daily living. A blood sample was collected after overnight fasting for measurement of HbA1c on the day immediately after the beginning of CGM. Patients were divided into three groups based on the measured level of HbA1c (< 7.0%, 7.0% ≤ HbA1c < 8.0% and ≥ 8.0%; control target set by the Japan Diabetes Society). The type, contents, timing and frequency of meals and exercise were not changed during CGM. None of the patients was on any medications that could affect glycemic control.
Parameters measured by continuous glucose monitoring

The average blood glucose level, SD of 24 hour glucose levels, rate of time spent in hypoglycemia (< 70 mg/dl), rate of time spent in hyperglycemia (> 180 mg/dl), maximum glucose level, minimum glucose level, pre-meal glucose level, 1 hour postprandial blood glucose level, 2 hour postprandial blood glucose level, postprandial peak glucose level, time to glucose peaks and range of glucose increases from pre-meal were measured from the data recorded by the CGM using a SMBG device (Medisafe mini, TERUMO, Tokyo, Japan). Previous studies indicated that interstitial glucose concentrations measured by the CGM correlate with venous blood glucose levels [6]. CGM measurements represent glucose concentrations in the interstitial fluid, but since the introduction of the SMBG technique, the measured value is considered to represent blood glucose level.

Other measurements

Venous blood samples were obtained in the morning following an overnight fast, and urinary C-peptide reactivity (CPR) levels in 24 hour urine collections were measured. Fasting plasma glucose levels were measured using a standard enzymatic method. Hemoglobin A1c (HbA1c)% was measured by high performance liquid chromatography (HPLC) using Tosoh HLC-723 G8 (Tosoh Co., Kyoto, Japan), and expressed as national glycohemoglobin standardization program (NGSP) values by adding 0.4% to HbA1c values expressed as the conventional Japanese standard substance (JDS) values [7]. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: [fasting plasma glucose (FPG) (mg/dl) × fasting plasma insulin (FPI) (μU/ml)] / 405. The homeostatic model assessment beta cell function (HOMA-β) was calculated as follows: [FPI (μU/ml) × 360/ (FPG (mg/dl) – 63)]. The estimate glomerular filtration rate (eGFR) was calculated as [194 × serum creatinine\(^{-1.094}\) × age\(^{-0.287}\)] for males and [194 × serum creatinine\(^{-1.094}\) × age\(^{-0.287}\) × 0.739] for females.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). The Fisher exact test was used to compare the categorical variables, and One-way analysis of variance (ANOVA), the Tukey honestly significant difference (HSD) test and the Games-Howell test were used to compare the continuous variables. Factors that could potentially correlate with CGM data were analyzed using Pearson correlation analysis for normally distributed parameters and Spearman rank correlation for variables with skewed distribution. Multivariate stepwise regression analysis was conducted using HbA1c, average glucose level and SD of 24 hour glucose levels as the dependent variables and several parameters found to be significantly related to HbA1c, average glucose level and SD of 24 hour glucose levels on univariate analysis. P values less than 0.05 were considered to reflect significant difference. All analyses were conducted using the PASW® statistics analysis software v19.0 (SPSS Inc, Chicago, IL).

Results

Patient demographics

The study sample included 71 T2DM patients (43 men and 28 women), with a mean age of 60.6 ± 14.3 years, and mean disease duration of 4.4 ± 6.9 years. The study patients were drug-naïve, and therefore were relatively young with shorter disease duration. Some patients, however, presented with microvascular complications on admission and long-standing untreated diabetes. The average HbA1c level was 8.1 ± 1.6%, indicating poor glycemic control, while the mean urinary CPR level was 85.5 ± 55.9 μg/day, indicating preservation of insulin secretion.

Continuous glucose monitoring data

The CGM data according to HbA1c levels indicated variability in the glycemic profile (Fig. 1). The average glucose level was 168 ± 40 mg/dl, and SD (glucose fluctuation) of 24 hour glucose levels was 33.9 ± 13.1 mg/dl, indicating large fluctuations. In addition, the maximum glucose level was 249 ± 59 mg/dl, and the percent time spent in hyperglycemia (> 180 mg/dl) was 32 ± 29%, indicating a higher percentage of hyperglycemia. Although the patients were drug naïve, the percentage of time spent in hypoglycemia (< 70 mg/dl) was 0.5 ± 1.8%, indicating that the glucose level of some patients was lower than 70 mg/dl.
Baseline characteristics and CGM data according to HbA1c

Patients were divided into three groups according to the HbA1c level (< 7.0% n = 23, 7.0% ≤ HbA1c < 8.0% n = 17 and ≥ 8.0% n = 31), and the baseline characteristics of each group were evaluated. With regard to glucose metabolism, patients of the HbA1c ≥ 8.0% group had higher fasting plasma glucose levels than the other two groups. With respect to the CGM data, patients in the HbA1c ≥ 8.0% group had higher average glucose level, maximum glucose level, minimum glucose level, and percent time spent in hyperglycemia (> 180 mg/dl) than the other two groups. However, there were no significant differences between the three groups in the SD of 24 hour glucose levels or percentage of time spent in hypoglycemia (< 70 mg/dl) (Table 1).

Analysis of CGM data before and after breakfast, lunch, and dinner

Analysis of data of the 71 patients indicated that the pre-meal glucose level was highest before lunch, and the 2 hour postprandial blood glucose level was lowest after lunch. In addition, the postprandial peak glucose level and the range of glucose increase from pre-meal to postprandial were lowest for lunch (Table 2).

The results of analysis according to HbA1c level indicated that the HbA1c ≥ 8.0% group had the highest pre-meal glucose level, and also had the highest 1 and 2 hour postprandial blood glucose and postprandial peak glucose levels. On the other hand, the range of increases in glucose from pre-meal to postprandial was highest for breakfast in the 7.0% ≤ HbA1c < 8.0% group, whereas the range at lunch and dinner were not significantly different between the three HbA1c groups. The ranges of increase in glucose from pre-meal to postprandial at breakfast and dinner were highest in the HbA1c ≥ 8.0% group, whereas the range at lunch was not significantly different between the three HbA1c groups. The time to glucose peak after breakfast was highest in the 7.0% ≤ HbA1c < 8.0% group, whereas the time periods to glucose peak after lunch and dinner were not significantly different between the three HbA1c groups, and corresponded to approximately 75–120 minutes after each meal in all three HbA1c groups, although this interval in the HbA1c < 7.0% group tended to be shorter (75–85 minutes) (Table 3).
### Table 1. Clinical characteristics of participants according to HbA1c level

| Clinical characteristics | HbA1c  < 7.0% | 7.0% ≤ HbA1c < 8.0% | ≥ 8.0% | P       |
|--------------------------|---------------|----------------------|--------|---------|
| Age (years)              | 59.7 ± 17.6   | 66.8 ± 12.1          | 58.0 ± 12.0 | 0.071   |
| Sex (male/female)        | 13 / 10       | 9 / 8                | 21 / 10 | 0.116   |
| Body mass index (kg/m²)  | 25.9 ± 5.8    | 29.1 ± 7.0           | 26.4 ± 6.5 | 0.262   |
| Abdominal circumference (cm) | 94.6 ± 11.2 | 101.0 ± 14.7         | 94.0 ± 10.8 | 0.166   |
| Duration of diabetes (years) | 3.9 ± 6.6   | 4.5 ± 8.3            | 4.6 ± 6.5 | 0.762   |
| Systolic blood pressure (mmHg) | 136.0 ± 20.1 | 138.2 ± 27.9         | 130.2 ± 14.0 | 0.729   |
| Diastolic blood pressure (mmHg) | 80.4 ± 15.3 | 82.6 ± 18.7          | 82.0 ± 8.2 | 0.555   |
| Triglyceride (mg/dl)     | 142.9 ± 55.6  | 180.2 ± 169.3        | 180.4 ± 107.3 | 0.475   |
| HDL-C (mg/dl)            | 46.1 ± 12.2   | 47.1 ± 11.9          | 47.5 ± 14.1 | 0.930   |
| LDL-C (mg/dl)            | 129.1 ± 39.4  | 127.9 ± 43.5         | 142.8 ± 42.4 | 0.423   |
| Fasting plasma glucose (mg/dl) | 119.4 ± 17.9 | 139.5 ± 27.7         | 172.3 ± 43.9 | < 0.001   |
| Fasting plasma insulin (µg/ml) | 10.6 ± 9.9   | 12.2 ± 5.0           | 9.5 ± 7.8 | 0.035   |
| HOMA-IR                  | 3.3 ± 3.5     | 4.3 ± 2.0            | 3.7 ± 3.1 | 0.039   |
| HOMA-β (%)               | 66.2 ± 45.3   | 69.7 ± 60.0          | 44.4 ± 56.0 | < 0.001   |
| u-CPR (µg/day)           | 80.3 ± 64.2   | 98.8 ± 51.4          | 82.5 ± 53.9 | 0.432   |
| eGFR (ml/min/1.73 m²)    | 78.6 ± 36.3   | 74.6 ± 31.0          | 71.1 ± 31.3 | 0.710   |
| CGM data                 |               |                      |        |         |
| Average glucose level (mg/dl) | 136.7 ± 20.8 | 167.9 ± 26.6         | 190.8 ± 40.9 | < 0.001   |
| SD of 24 hour glucose levels (mg/dl) | 29.7 ± 9.0 | 32.0 ± 10.0          | 38.0 ± 16.1 | 0.072   |
| Maximum glucose level (mg/dl) | 219.9 ± 35.5 | 244.6 ± 39.5         | 273.6 ± 70.5 | 0.002   |
| Minimum glucose level (mg/dl) | 92.8 ± 17.9 | 117.0 ± 17.8         | 123.2 ± 44.5 | < 0.001   |
| Time spent in hyperglycemia (> 180 mg/dl) (%) | 12.5 ± 11.4 | 31.9 ± 22.7          | 46.8 ± 32.0 | < 0.001   |
| Time spent in hypoglycemia (< 70 mg/dl) (%) | 0.3 ± 1.7   | 0.1 ± 0.5            | 0.8 ± 2.2 | 0.248   |
| Diabetic microvascular complications, n (%) |               |                      |        |         |
| neuropathy               | 1 (4)         | 8 (47)               | 15 (48) | < 0.001 |
| retinopathy              | 0 (0)         | 2 (12)               | 5 (16)  | 0.138   |
| nephropathy              | 2 (9)         | 3 (18)               | 7 (23)  | 0.402   |
| Diabetic macrovascular complication number (%) | 0 (0)         | 1 (6)                | 3 (10)  | 0.312   |

Data are mean ± standard deviation (SD) or n (%). The Fisher exact test was used to compare categorical variables, and One-way analysis of variance (ANOVA), the Tukey honestly significant difference (HSD) test and the Games-Howell test were used to compare continuous variables. HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment insulin resistance, HOMA-β: homeostasis model assessment β, u-CPR: urine C-peptide immunoreactivity, eGFR: estimated glomerular filtration rate, CGM: continuous glucose monitoring.

### Table 2. The summary of glycemic profiles of each meal

| Glycemic profile | Breakfast | Lunch | Dinner | P       |
|------------------|-----------|-------|--------|---------|
| Pre-meal glucose level (mg/dl) | 143.0 ± 30.3 | 163.7 ± 56.6 | 142.3 ± 40.9 | 0.019 |
| 1 hour postprandial blood glucose level (mg/dl) | 204.3 ± 54.0 | 196.1 ± 54.7 | 211.1 ± 44.5 | 0.216 |
| 2 hour postprandial blood glucose level (mg/dl) | 215.7 ± 61.0 | 190.3 ± 55.3 | 216.1 ± 53.9 | 0.009 |
| Postprandial peak glucose level (mg/dl) | 235.0 ± 57.6 | 214.1 ± 55.5 | 236.1 ± 54.1 | 0.032 |
| Time to glucose peak (min) | 102.8 ± 42.0 | 89.9 ± 42.3 | 89.3 ± 38.8 | 0.090 |
| Range of glucose increases from pre-meal (mg/dl) | 91.9 ± 39.8 | 50.3 ± 26.1 | 93.9 ± 43.0 | < 0.001 |

All values are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA), the Tukey honestly significant difference (HSD) and the Games-Howell test were used to compare continuous variables.
Factors associated with HbA1c, average glucose and SD of 24 hour glucose levels of glucose in CGM

Univariate analysis of the relationship between HbA1c and CGM parameters indicated that variables other than the percentage time spent in hypoglycemia (<70 mg/dl) and time to glucose peak correlated with HbA1c. Multivariate analysis identified the average glucose level as the most significant and independent determinant of HbA1c (r = 0.740) (Table 4).

Next we evaluated the relationship between average glucose and CGM parameters at each meal. Univariate analysis demonstrated that all the tested variables, with the exception of range of glucose increase from pre-meal at lunch and dinner, correlated significantly with the average glucose level. Multivariate analysis of the above factors identified pre-meal glucose level at dinner (r = 0.319) and 2 hour postprandial blood glucose level in the morning (r = 0.216) as the significant and independent determinants (Table 4). Further analysis identified pre-meal glucose level at lunch (r = 0.505) and postprandial peak glucose level in the morning (r = 0.377) and pre-meal glucose level at dinner (r = 0.310) as significant determinants of HbA1c level in the HbA1c < 7.0% group (Table 4). Pre-meal glucose level at lunch (r = 0.658), 1 hour postprandial blood glucose level at dinner (r = 0.525) and time to glucose peaks in the morning (r = -0.216) were significant determinants in the 7.0% ≤ HbA1c < 8.0% group (Table 3). Pre-meal glucose level at dinner (r = 0.375), 1 hour postprandial blood glucose level at lunch (r = 0.325), 2 hour postprandial blood glucose level in the morning (r = 0.240), and pre-meal glucose level in the morning (r = 0.190) were significant determinants in the HbA1c ≥ 8.0% group (Table 4).

The relationship between SD of 24 hour glucose
levels and CGM parameters at each meal was also examined. Univariate analysis indicated that all variables, except the time to glucose peak, correlated with SD of 24 hour glucose levels. Multivariate analysis identified the range of glucose increase from pre-meal in the morning \( (r = 0.341) \) and dinner \( (r = 0.385) \) as significant and independent determinants of SD of 24 hour glucose levels (Table 5). Further analysis indicated that SD of 24 hour glucose levels was significantly and independently associated with the range of glucose increase from pre-meal in the morning \( (r = 0.679) \) in the HbA1c < 7.0% group (Table 5), the range of glucose increase from pre-meal in the morning \( (r = 0.544) \) in the 7.0% ≤ HbA1c < 8.0% group (Table 5), and the postprandial peak glucose level at lunch \( (r = 0.570) \) and range of glucose increase from pre-meal at dinner \( (r = 0.511) \) in the HbA1c ≥ 8.0% group (Table 5).

Table 4. Results of multivariate analysis with HbA1c and average glucose level as the dependent variables

| Variables | Non-standardized coefficients | Standardized coefficients | P value | 95%CI |
|-----------|--------------------------------|---------------------------|---------|-------|
| HbA1c as the dependent variable | | | | |
| Intercept | 3.126 | <0.001 | 2.003 | 4.249 |
| Average glucose level | 0.030 | 0.740 | <0.001 | 0.024 | 0.037 |
| Adjusted multiple R² | | | 0.541 |
| Average glucose level as the dependent variable - all patients | | | | |
| Intercept | -3.714 | 0.487 | -14.323 | 6.895 |
| pre-meal glucose level at lunch | 0.092 | 0.130 | 0.041 | 0.004 | 0.179 |
| 2 hour postprandial blood glucose level in the morning | 0.140 | 0.216 | <0.001 | 0.088 | 0.192 |
| pre-meal glucose level at dinner | 0.311 | 0.319 | <0.001 | 0.236 | 0.386 |
| pre-meal glucose level at breakfast | 0.242 | 0.184 | <0.001 | 0.150 | 0.333 |
| 1 hour postprandial blood glucose level at dinner | 0.096 | 0.108 | 0.004 | 0.032 | 0.161 |
| postprandial peak glucose level at lunch | 0.121 | 0.169 | 0.005 | 0.039 | 0.204 |
| Adjusted multiple R² | | | 0.967 |
| Average glucose level as the dependent variable in HbA1c < 7.0% group | | | | |
| Intercept | 24.144 | 0.004 | 8.803 | 39.484 |
| pre-meal glucose level at lunch | 0.350 | 0.505 | <0.001 | 0.221 | 0.480 |
| postprandial peak glucose level in the morning | 0.185 | 0.377 | <0.001 | 0.118 | 0.252 |
| pre-meal glucose level at dinner | 0.267 | 0.310 | 0.001 | 0.126 | 0.408 |
| Adjusted multiple R² | | | 0.936 |
| Average glucose level as the dependent variable in 7.0% ≤ HbA1c < 8.0% group | | | | |
| Intercept | 23.548 | 0.075 | -2.733 | 49.828 |
| pre-meal glucose level at lunch | 0.459 | 0.658 | <0.001 | 0.322 | 0.597 |
| 1 hour postprandial blood glucose level at dinner | 0.428 | 0.525 | <0.001 | 0.271 | 0.584 |
| Time to glucose peaks in the morning | -0.130 | -0.216 | 0.021 | -0.237 | -0.024 |
| Adjusted multiple R² | | | 0.915 |
| Average glucose level as the dependent variable in HbA1c ≥ 8.0% group | | | | |
| Intercept | 1.140 | 0.887 | -15.209 | 17.489 |
| 2 hour postprandial blood glucose level in the morning | 0.169 | 0.240 | <0.001 | 0.088 | 0.250 |
| pre-meal glucose level at dinner | 0.329 | 0.375 | <0.001 | 0.233 | 0.426 |
| 1 hour postprandial blood glucose level at lunch | 0.233 | 0.325 | <0.001 | 0.144 | 0.323 |
| pre-meal glucose level in the morning | 0.256 | 0.190 | 0.001 | 0.112 | 0.400 |
| Adjusted multiple R² | | | 0.961 |

Multivariate stepwise regression analysis was conducted using HbA1c and average glucose level as the dependent variables, and several parameters were found to be significantly related to HbA1c and average glucose level on univariate analysis. All were measured by the continuous glucose monitoring system. \( R^2 \): coefficient of determination, HbA1c: hemoglobin A1c
The present study evaluated the glycemic profile of 71 drug-naive T2DM patients using CGM, and examined factors associated with HbA1c, mean blood glucose level and SD of 24 hour glucose levels. In these patients, the pre-meal glucose level was highest before lunch, while the postprandial peak glucose level was highest after breakfast and dinner. The range of glucose increase from before to after a meal was highest for breakfast and dinner, and the time to peak glucose was 90–110 minutes. In addition, the pre-meal glucose level, postprandial peak glucose level and the range of glucose increase from before to after meal at lunch and dinner and time to peak glucose were independent of HbA1c.

A few studies analyzed the CGM data of T2DM patients [8, 9], but the patients in these studies were on treatment for diabetes, and therefore the effects of drugs on the results could not be excluded. Wang et al evaluated drug-naive T2DM patients by CGM and compared them to subjects with normal glucose tolerance and another group of subjects with impaired glycemic control [4]. Ando et al performed a detailed analysis of the glycemic profiles of drug-naive T2DM patients and reported that the pre-meal glucose level and postprandial peak glucose level at each meal increased with increases in HbA1c levels, whereas the range of glucose increase from before to after meal was independent of HbA1c [5]. Our results confirmed the latter finding. With regard to the time to glucose peak, Ando et al reported that this interval at breakfast and dinner increased with increases in HbA1c, whereas such correlation was found only at breakfast in the

### Table 5. Results of multivariate analysis with standard deviation (SD) of 24 hour glucose levels as the dependent variables

| Variables                                      | Non-standardized coefficients | Standardized coefficients | P value | 95%CI |
|------------------------------------------------|-------------------------------|---------------------------|---------|-------|
| SD of 24 hour glucose levels as the dependent variable - all patients |                               |                           |         |       |
| Intercept                                      | -5.603                        | 0.069                     | -11.665 | 0.459 |
| Range of glucose increases from pre-meal in the morning | 0.111                         | 0.341                     | <0.001  | 0.058 | 0.164 |
| Range of glucose increases from pre-meal at dinner | 0.113                         | 0.385                     | <0.001  | 0.076 | 0.149 |
| Postprandial peak glucose level at lunch        | 0.071                         | 0.314                     | <0.001  | 0.036 | 0.105 |
| Time to glucose peaks at dinner                 | 0.048                         | 0.151                     | 0.013   | 0.010 | 0.085 |
| Adjusted multiple R²                            |                              |                           |         | 0.781 |
| SD of 24 hour glucose levels as the dependent variable in HbA1c <7.0% group |                               |                           |         |       |
| Intercept                                      | -7.069                        | 0.130                     | -16.410 | 22.719|
| Range of glucose increases from pre-meal in the morning | 0.186                         | 0.679                     | <0.001  | 0.133 | 0.2404|
| 1 hour postprandial blood glucose level at dinner | 0.100                         | 0.376                     | 0.001   | 0.048 | 0.153 |
| Time to glucose peaks at lunch                  | 0.041                         | 0.193                     | 0.035   | 0.003 | 0.079 |
| Adjusted multiple R²                            |                              |                           |         | 0.841 |
| SD of 24 hour glucose levels as the dependent variable in 7.0% ≤ HbA1c < 8.0% group |                               |                           |         |       |
| Intercept                                      | -4.393                        | 0.552                     | -19.842 | 11.055|
| Range of glucose increases from pre-meal in the morning | 0.155                         | 0.544                     | 0.005   | 0.055 | 0.256 |
| Postprandial peak glucose level at lunch        | 0.115                         | 0.428                     | 0.021   | 0.021 | 0.210 |
| Adjusted multiple R²                            |                              |                           |         | 0.742 |
| SD of 24 hour glucose levels as the dependent variable in HbA1c ≥ 8.0% |                               |                           |         |       |
| Intercept                                      | -10.400                       | 0.136                     | -24.267 | 3.467 |
| Range of glucose increases from pre-meal at dinner | 0.141                         | 0.511                     | <0.001  | 0.081 | 0.201 |
| Postprandial peak glucose level at lunch        | 0.140                         | 0.570                     | <0.001  | 0.087 | 0.193 |
| Adjusted multiple R²                            |                              |                           |         | 0.679 |

Multivariate stepwise regression analysis was conducted using SD of 24 hour glucose levels as the dependent variables, and several parameters were found to be significantly related to SD of 24 hour glucose levels on univariate analysis. All were measured by the continuous glucose monitoring system. R²: coefficient of determination, HbA1c: hemoglobin A1c.
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The present study [5]. Taken together, we suggest that postprandial peak glucose level should be measured 90 to 110 minutes after meals in Japanese T2DM patients. Another interesting finding in our study was that postprandial peak glucose level tended to be lower after lunch, compared with breakfast and dinner, which was considered a characteristic feature of T2DM. We assume that this finding could have been influenced by the second meal phenomenon [10]. We believe that the control of blood glucose level after breakfast and dinner is necessary in order to achieve a more strict control of glucose level, and that strict dietary regimens for breakfast and dinner could reduce glycemic variability within a day.

Our results showed that HbA1c level did not correlate with the range of glucose increase from before to after a meal at lunch and dinner. This result indicates that the increase in postprandial blood glucose level in individuals with HbA1c levels lower than 7.0% was similar to that in individuals with HbA1c of 8.0% or higher. Suh et al showed that the glycemic variability is correlated with total glucose exposure only in well-controlled T2DM [11]. Monnier et al reported that the relative contribution of postprandial blood glucose to HbA1c level was approximately 70% in patients with HbA1c levels lower than 7.3%, and that postprandial blood glucose and fasting blood glucose had similar contribution to HbA1c in patients with HbA1c of 7.3–8.4%, while fasting blood glucose had greater influence on HbA1c than postprandial blood glucose in patients with HbA1c of 8.5% or higher, and this tendency increased with increases in HbA1c level [12]. Similar results were obtained in the present study, where glucose level before each of the three meals was approximately 120 mg/dl. However, the postprandial peak glucose level was 180–200 mg/dl in patients with HbA1c levels lower than 7.0%; the pre-meal glucose level was 140–160 mg/dl and postprandial peak glucose level was 220 mg/dl in subjects with 7.0% ≤ HbA1c < 8.0%; and the pre-meal glucose level was 160–200 mg/dl and postprandial peak glucose level was 260 mg/dl in patients with HbA1c of 8.0% or higher, indicating increases in pre-meal glucose levels with increases in HbA1c level. We considered the reason why the correlated factor differs in group analysis of HbA1c as follows. All the subjects in this study were drug naïve cases with short diabetes morbidity duration, and insulin secretion still remained. However, HOMA - β clearly decreased to 44.4% in the HbA1c ≥ 8.0% group, compared to 66.2% in HbA1c < 7.0% and 69.7% in 7.0% ≤ HbA1c < 8.0% group. In the early stage of diabetes, the initial secretion of insulin decreases and postprandial hyperglycemia is recognized. As the diabetes progresses, insulin secretion decreases gradually, leading to higher levels of blood glucose after breakfast and before lunch. A further decrease of insulin secretion is followed by increased blood glucose level after lunch and before dinner.

Our study has several limitations. First, the sample size was relatively small. Second, since the subjects were inpatients, their glycemic control may have improved after admission because of the diet and exercise programs provided during hospitalization, thus indirectly affecting HbA1c levels after admission. Third, changes in motivation correlated with the use of CGM might have affected blood glucose levels of the participants. Fourth, since the CGM data were obtained within a short period immediately after admission, we need to assess the long-term relevance of these findings. Fifth, the glucose data from CGM were not the same as those of blood glucose measurements. We noted that in some cases, blood glucose levels of ≥ 400 mg/dl or ≤ 40 mg/dl were beyond the measurement limits of the CGM device. Further studies of larger samples are needed to confirm our findings and to determine their effects on drug selection and glycemic control.

In conclusion, improvement of the average glucose level is necessary to improve the HbA1c levels. For patients with HbA1c < 7.0%, it is important to improve blood glucose level after breakfast and before lunch to decrease the average glucose level. For patients with 7.0% ≤ HbA1c < 8.0%, it is important to improve blood glucose level before lunch and after dinner to decrease the average glucose level. For patients with HbA1c ≥ 8.0%, it is important to improve blood glucose levels after lunch and before dinner to decrease the average glucose level.

Acknowledgments

The authors thank Ms. N. SAKAGUCHI for the excellent technical assistance.
Disclosure

Y Tanaka has received speaking fees and/or honoraria from Daiichi-Sankyo, Astellas, Pfizer, Mitsubishi-Tanabe, Bristol-Myers, Chugai, YL Biologics, Eli Lilly, Sanofi, Janssen and UCB, and has received research grants from Mitsubishi-Tanabe, Takeda, Bristol-Myers, Chugai, Astellas, Abbvie, Merck Sharp and Dohme (MSD), Daiichi-Sankyo, Pfizer, Kyowa-Kirin, Eisai and Ono. Y Okada, has received speaking fees and/or honoraria from MSD, Astellas, Mitsubishi-Tanabe, Eli Lilly, Takeda, Ono, Novo and Bayer, and has received research grants from Mitsubishi-Tanabe and Kowa. The other authors declare no conflict of interest.

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薬物が投与されていない2型糖尿病患者における持続的血糖モニタリングの分析

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要 旨：薬物が投与されていない2型糖尿病患者のHbA1cによる血糖プロファイルをCGM（continuous glucose monitoring）を用いて検討した。本研究においてHbA1c, 平均血糖値に影響する因子を明らかにすることを目的とした。対象患者をHbA1cによって3群に分け(< 7.0% n = 23, 7.0% ≤ HbA1c < 8.0% n = 17 and ≥ 8.0% n = 31), それぞれの群でHbA1c, 平均血糖値と関連する因子を解析した。食前血糖は昼食前がもっとも高値で, 食後血糖値は昼食後がもっとも低値であった。HbA1cの悪化とともに, 全食事においても食前, 食後血糖値は上昇していた。もっとも強く関連する因子は, HbA1cは平均血糖値, 平均血糖値は夕食前血糖値, 血糖変動は夕食時血糖上昇幅であった。HbA1cのグループ解析では, 平均血糖値もっとも強く関連する因子は, HbA1c< 8.0%群は, 昼食前血糖値, HbA1c ≥ 8.0%群は, 夕食前血糖値, 血糖変動にもっとも強く関連する因子は, HbA1c< 8.0%群は朝食時血糖上昇幅, HbA1c ≥ 8.0%群は昼食後最高血糖値であった。以上の結果は, HbA1cの改善には平均血糖値の改善が重要であった。平均血糖値を改善するために, HbA1c< 7.0%では, 朝食後, 昼食前血糖値を, 7.0% ≤ HbA1c < 8.0%では昼食前, 夕食後血糖値を, HbA1c ≥ 8.0%では, 昼食後, 夕食前血糖値を改善することが重要である。

キーワード：持続血糖モニタリング, 薬物投与なし, 2型糖尿病

J UOEH (産業医大誌) 40(4): 287 ~ 297 (2018)