

# Relationship Between Glycemic Intraday Variations Evaluated in Continuous Glucose Monitoring and HbA1c Variability in Type 2 Diabetes: Pilot Study

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## Research

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# Abstract

**Background:** HbA1c variability is independent of mean HbA1c, and associated with mortality due to vascular complications. However, the significance of HbA1c variability is unknown at present. In this study, we used flash glucose monitoring (FGM) and evaluated glycemic intraday variations, and then examined the association with HbA1c variability.

**Methods:** We conducted a retrospective pilot study of 26 patients treated at the Outpatient department for type 2 diabetes mellitus (T2DM), and evaluated the following items associated with blood glucose levels and their changes/variations using FGM. The primary endpoint was factor(s) associated with Standard deviation (SD) HbA1c over a six-month period.

**Results:** There were significant correlations between mean HbA1c and each of glucose management indicator, maximum, percent time at glucose >180 mg/d, mean of daily difference of blood glucose, and high blood glucose index. SD HbA1c correlated significantly with percent time at glucose <70 mg/dL and low blood glucose index. We estimated the regression coefficient of SD HbA1c using multivariate linear regression analysis, and noted that the presence of hypoglycemia affected SD HbA1c ( $\beta=0.132$ ,  $SE=0.055$ ,  $P=0.026$ ). Hypoglycemia was noted in 17 patients, and SD HbA1c was significantly higher ( $p<0.001$ ) in the hypoglycemic group ( $0.24\pm0.13\%$ ), compared with the non-hypoglycemic group ( $0.09\pm0.06\%$ ). The cut-off value of SD HbA1c was 0.126% in the hypoglycemic group.

**Conclusions:** The results showed that HbA1c variability is associated with hypoglycemia. HbA1c variability reflects the risk of hypoglycemia, suggesting a possible association with the risk of cardiovascular mortality. For patients with high HbA1c variability, we recommend evaluation for the presence of hypoglycemia and reconsideration of their treatment regimen including their glucose-lowering medications.

**Trial registration:** The study protocol and opt-out method of informed consent were approved by the ethics committees of the University of Occupational and Environmental Health (Trial registration: H27-186, Registered 25 Dec 2015).

## Background

One of the objectives of treatment of diabetes is prevention of future diabetes-related complications through glycemic control. HbA1c is the gold standard index used for monitoring the effectiveness of treatment of diabetes. HbA1c reflects blood glucose level over the previous two months, and it is not affected by short periods of blood glucose variations, such as following meals and exercise [1]. In this regard, Continuous Glucose Monitoring (CGM) and Flash Glucose Monitoring (FGM) have been recommended for managing more specific glucose levels, and the time in range (TIR) and blood glucose levels of 180 or above and under 70 have become international standards for monitoring the response to diabetes treatment [2]. While CGM is a useful supplementary device, it is difficult to use in all patients during routine clinical practice.

Clinical evidence indicates that the use of HbA1c is clearly beneficial in the prevention of microangiopathy. The Diabetes Control and Complications Trial (DCCT) group has reported that the use of HbA1c as an index of glycemic control slows down the progression of diabetic retinopathy, nephropathy and neuropathy [3]. Furthermore, the effects of intensive glucose-lowering therapy on blood pressure and albumin excretion were still evident at 7 to 8 years after the end of the DCCT study; suggesting the effects of prevention of progression of diabetic nephropathy was also being maintained [4]. Furthermore, the United Kingdom Prospective Diabetes Study (UKPDS) showed that for each 1% drop in HbA1c, the risk of microvascular complications reduces by 37% [5]. These trials verified the importance of elevated HbA1c as an indicator of chronic hyperglycemia. Another detailed blood glucose profile study using CGM concluded that HbA1c reflects the mean blood glucose level [6].

The ADVANCE trial [7] examined the effect of glycemic control, using HbA1c as the index parameter, and reported that intensive glucose-lowering therapy was not associated with a significant reduction in macrovascular disorders. Furthermore, the ACCORD trial concluded that intensive therapy was associated with significantly higher all-cause mortality and cardiovascular mortality hazard ratios [8]. These studies suggest that serious hypoglycemia linked to intensive therapy may underlie the increased risk of mortality. In this regard, recent studies have reported that large swings in blood glucose levels are associated with worsening of arteriosclerosis [9] and increased risk of mortality due to cardiovascular events [10]. Apart from blood glucose levels, the correlation between HbA1c variability, in addition to mean HbA1c, and mortality due to diabetic vasculopathies has also been analyzed [11–13]. However, to date, the true significance of HbA1c variability remains unknown.

We hypothesized that HbA1c variability is associated with glycemic profile in diabetes patients, and that it is associated with macrovascular-related mortality. To test this hypothesis, we used the FGM system to examine the relationship between HbA1c variability and detailed glycemic profiles.

## Methods

### Subjects

We conducted a retrospective study from September 2018 to January 2019 at the Outpatient Clinic of the University of Occupational Medicine Hospital and University of Occupational Medicine Wakamatsu Hospital. The subjects were 26 patients with type 2 diabetic mellitus (T2DM), who had been on the FGMS® System (FreeStyle Libre Pro System, Abbott Diabetes Care, Inc.) for at least eight days for evaluation of hemodynamics. The following inclusion criteria were applied in this study: 1) age between 30-to-80 years at the time of obtaining consent; 2) T2DM treated and followed-up at the Outpatients Clinic; 3) no changes (addition, switching, or discontinuation) to the glucose-lowering agents or their doses within the 4-week period before the commencement of the FGMS; 4) no changes to the T2DM treatment up to 6 months after the start of FGM. The following exclusion criteria were also applied. 1) Type 1 or secondary diabetes mellitus; 2) severe infection, before- or after surgery, or serious trauma; 3) renal dialysis; 4) severe hepatic dysfunction (AST  $\geq$  100 IU/l); 5) moderate or severe heart failure

(NYHA/New York Heart Association Classification III or higher stage); and 6) pregnant, lactating, or potentially pregnant patients. The primary endpoint was factor(s) associated with HbA1c variability over a six-month period, and the secondary endpoint was factor(s) associated with mean HbA1c.

The study protocol and opt-out method of informed consent were approved by the ethics committees of the University of Occupational and Environmental Health (Trial registration: H27-186, Registered 25 Dec 2015).

## Flash glucose monitoring system

The following parameters were measured using the data recorded by the FGM: average glucose level (AG), standard deviation (SD), coefficient of variation (CV), percent time at glucose level of 70–180 mg/dl (TIR: time in range), percent time at > 180 mg/dl (TAR: time above range), percent time < 70 mg/dl (TBR: time below range), maximum, minimum, glucose management indicator (GMI) [14], mean daily difference of blood glucose (MODD), low blood glucose index (LBGI) and high blood glucose index (HBGI) [15]. Hypoglycemia was defined as a glucose value less than 70 mg/dL as recorded by FGM. The FGM data were recorded to avoid bias due to the insertion and removal of the FGM, or lack of stability of the unit. The sensors were applied for seven consecutive days, starting from the second day (excluding the first day of wearing the sensor). We recorded the daily average value, and listed the average value for seven days.

## Laboratory tests

HbA1c (%) was measured by HPLC using Tosoh HLC-723 G8 (Tosoh Co., Kyoto, Japan) and recorded as a NGSP (National Glycohemoglobin Standardization Program) value. eGFR (estimated glomerular filtration rate) was calculated as  $194 \times \text{serum creatinine concentration (mg/dl)} - 1.094 \times \text{age} - 0.287$  for men, and  $194 \times \text{serum creatinine concentration (mg/dl)} - 1.094 \times \text{age} - 0.287 \times 0.739$  for women. The SD HbA1c represents the SD of 3–7 HbA1c readings over a 6-month period from the time of starting the use of FGM, and the mean HbA1c is the mean of the same measurements.

## Statistical analysis

Values are shown as mean  $\pm$  standard deviation. The Shapiro-Wilk test was used to test for normality; for statistical significance of the mean values of two groups, the Student's t-test was used if equal variance was confirmed by the F test, whereas Welch's t-test was used if it followed normal distribution. The Mann-Whitney U test was used if it did not follow a normal distribution, and Spearman's correlation analysis was used for testing the relationship between two variables. Univariate and multivariate linear regression analyses were used to estimate the regression coefficients for SD HbA1c. Multivariate analysis was performed with SD HbA1c as the dependent variable, and gender, age, BMI, eGFR, number of glucose-lowering agents, and presence of hypoglycemia as independent variables. The cutoff value of SD HbA1c was examined based on the ROC curve. The calculated sample size in the ROC analysis was 30 patients in total, assuming an area under the curve (AUC) of 0.80, power 0.80, with significance level of 5%, and a

non-hypoglycemic group versus the hypoglycemic group of 2:1. A  $p$  value  $< 0.05$  was considered significant. All analyses were performed using SPSS Statistical Software 25.0 (SPSS Inc., Chicago, IL).

## Results

### Clinical characteristics of study participants

The clinical characteristics are shown in Table 1. The study participants were 26 patients (14 males, 12 females) aged  $68.5 \pm 7.8$  years (range, 51–79 years), with BMI of  $24.3 \pm 4.1$  kg/m<sup>2</sup>, HbA1c  $6.7 \pm 0.6\%$  (5.7–7.7%), SD HbA1c  $0.19 \pm 0.13\%$  (0.00–0.51%), mean HbA1c  $6.8 \pm 0.6\%$  (5.7–7.8%), and history of diabetes of  $12.6 \pm 10.0$  years (1.3–30 years). As for the antidiabetic agents, 65% of patients were using DPP-4 inhibitors while 46% were using biguanide.

Table 1  
Baseline characteristics and CGM parameters of the 26 patients.

	mean ± SD
Sex (male/female)	14/12
Age (year)	68.5 ± 7.8
Height (cm)	159.9 ± 8.2
Weight (kg)	62.5 ± 13.9
BMI (kg/m <sup>2</sup> )	24.3 ± 4.1
SBP (mmHg)	136.4 ± 16.8
DBP (mmHg)	73.7 ± 9.6
Duration of diabetes (years)	12.6 ± 10.0
HbA1c (%)	6.7 ± 0.6
Creatinine (mg/dL)	0.85 ± 0.23
eGFR (mL/min/1.73m <sup>2</sup> )	63.9 ± 14.2
Neuropathy [n (%)]	5 (19)
Retinopathy [n (%)]	2 (8)
Nephropathy [n (%)]	6 (23)
Diabetes treatment	
Diet only [n (%)]	1 (4)
SU [n (%)]	0
Glinide [n (%)]	2 (8)
DPP-4 inhibitor [n (%)]	17 (65)
Biguanide [n (%)]	12 (46)
Thiazolidine [n (%)]	5 (19)
SGLT-2 inhibitor [n (%)]	7 (27)
α-glucose inhibitor [n (%)]	5 (19)

BMI, Body Mass Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate; SU, sulfonylureas; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor, sodium-glucose transporter-2 inhibitor; GLP-1 receptor, Glucagon-like peptide-1 receptor; CGM, Continuous Glucose Monitoring; MODD, mean of daily difference of blood glucose; SD, standard deviation; CV, coefficient of variation; TBR, Time below range; TIR, Time in range; TAR, Time above range; LBGI, low blood glucose index; HBGI, high blood glucose index.

	mean ± SD
GLP-1 receptor [n (%)]	3 (12)
Insulin [n (%)]	2 (8)
CGM parameters	
Average glucose (mg/dL)	129.2 ± 21.1
MODD (mg/dL)	27.5 ± 9.5
SD (mg/dL)	33.1 ± 8.7
CV (%)	25.6 ± 4.7
Maximum (mg/dL)	214.0 ± 36.8
Minimum (mg/dL)	81.3 ± 15.4
TBR (%)	1.5 ± 2.5
TIR (%)	87.1 ± 11.8
TAR (%)	11.4 ± 11.8
LBGI	1.6 ± 1.1
HBGI	4.2 ± 2.3
BMI, Body Mass Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate; SU, sulfonylureas; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; SGLT-2 inhibitor, sodium-glucose transporter-2 inhibitor; GLP-1 receptor, Glucagon-like peptide-1 receptor; CGM, Continuous Glucose Monitoring; MODD, mean of daily difference of blood glucose; SD, standard deviation; CV, coefficient of variation; TBR, Time below range; TIR, Time in range; TAR, Time above range; LBGI, low blood glucose index; HBGI, high blood glucose index.	

## Factors associated with SD HbA1c

Table 2 shows the correlation between SD HbA1c and each of the listed factors. There was significant correlation between SD HbA1c and TBR ( $r = 0.507$ ,  $P = 0.008$ ; Fig. 1A), and between SD HbA1c and LBGI ( $r = 0.462$ ,  $P = 0.018$ ; Fig. 1B). There was no significant difference in SD HbA1c between with and without each drug (Supplemental Table 1).

Table 2  
Correlation with SD HbA1c and mean HbA1c.

	SD HbA1c		mean HbA1c	
	$\rho$	P value	$\rho$	P value
Average glucose (mg/dL)	-0.251	0.217	0.624	0.001*
SD (mg/dL)	0.027	0.896	0.463	0.017*
CV (%)	0.288	0.153	0.266	0.190
GMI (%)	-0.251	0.217	0.624	0.001*
Maximum (mg/dL)	-0.207	0.311	0.467	0.016*
Minimum (mg/dL)	-0.379	0.056	0.319	0.113
TBR (%)	0.507	0.008*	-0.184	0.369
TIR (%)	0.142	0.493	-0.445	0.023*
TAR (%)	-0.241	0.235	0.525	0.006*
MODD (mg/dL)	-0.067	0.744	0.570	0.002*
LBGI	0.462	0.018*	-0.165	0.421
HBGI	-0.143	0.485	0.452	0.021*
The FGM data used seven consecutive days, and the values in the table represent the average of seven days.				
Data are results of Spearman rank correlation. Correlation is significant at $p < 0.05^*$ .				
SD, standard deviation; CV, coefficient of variation; GMI, Glucose Management Indicator; TBR, Time below range (< 70 mg/dl); TIR, Time in range (70–180 mg/dL); TAR, Time above range (> 180mg/dL); MODD, mean of daily difference of blood glucose; LBGI, low blood glucose index; HBGI, high blood glucose index.				

Univariate and multivariate linear regression analyses were used to estimate the regression coefficients for SD HbA1c (Table 3). Furthermore, multivariate analysis with SD HbA1c as the dependent variable, and gender, age, BMI, eGFR, number of anti-diabetes medications, and the presence of hypoglycemia as independent variables; identified the presence of hypoglycemia as the single significant determinant of SD HbA1c ( $\beta = 0.132$ ,  $SE = 0.055$ ,  $P = 0.026$ ).

Table 3  
Linear multivariable analysis with SD HbA1c as the dependent variable.

	Univariable linear regression			Multivariable linear regression		
	$\beta$	SE	P	$\beta$	SE	P
Intercept				0.700	0.535	0.206
Sex, man/women	-0.038	0.054	0.481	-0.012	0.049	0.807
Age, years	0.001	0.004	0.768	-0.003	0.004	0.437
Height	0.002	0.003	0.495			
Weight	-0.001	0.002	0.458			
BMI, kg/m <sup>2</sup>	-0.008	0.007	0.228	-0.009	0.008	0.303
SBP	0.001	0.002	0.384			
DBP	0.002	0.003	0.417			
Duration of diabetes	-0.003	0.003	0.286			
HbA1c	-0.019	0.047	0.693			
Creatinine	0.082	0.118	0.496			
eGFR	-0.001	0.002	0.544	-0.002	0.002	0.390
Number of anti-diabetic agents	-0.026	0.026	0.334	-0.012	0.024	0.623
Hypoglycemia, yes/no	0.154	0.047	0.003*	0.132	0.055	0.026*
We used univariable and multivariable linear regression analysis to estimate regression coefficients for SD HbA1c. The model fed into hypoglycemia. We selected one of the similar indicators from which multicollinearity may occur for each factor and examined in two models.						
$\beta$ , regression coefficient; SE, standard error; CI, confidence interval; BMI, Body Mass Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate.						

## Factors associated with mean HbA1c

Table 2 shows the correlation between HbA1c and each factor. There were significant correlations between mean HbA1c and each of GMI ( $r = 0.624$ ,  $P = 0.001$ ), maximum ( $r = 0.467$ ,  $P = 0.016$ ), TAR ( $r = 0.525$ ,  $P = 0.006$ ), MODD ( $r = 0.570$ ,  $P = 0.002$ ), and HBGI ( $r = 0.452$ ,  $P = 0.021$ ; Fig. 1C). On the other hand, there was a negative correlation between mean HbA1c and TIR ( $r = -0.445$ ,  $P = 0.023$ ; Fig. 1D).

## Hypoglycemia versus non-hypoglycemia

We examined the difference between SD HbA1c and mean HbA1c with and without hypoglycemia (Fig. 2a, 2b). SD HbA1c was significantly higher in the hypoglycemic group ( $p < 0.001$ ) at  $0.24 \pm 0.13\%$ , compared to the non-hypoglycemic group at  $0.09 \pm 0.06\%$ . On the other hand, there was no significant difference in mean HbA1c between with or without hypoglycemia.

In order to evaluate the cutoff of SD HbA1c in the hypoglycemic group, a ROC curve was constructed and the area under the curved surface was calculated. ROC curve analysis showed a cutoff value of SD HbA1c of  $0.126\%$  (area under the curve =  $0.895$ ,  $95\%CI$   $0.764-1.000$ ) in the hypoglycemic group. Comparison of the number of patients with hypoglycemia below or above the SD HbA1c cutoff value showed significantly higher number of hypoglycemic patients in the SD HbA1c  $\geq 0.126\%$  group ( $p = 0.001$ , Fig. 2c).

## Discussion

We conducted a pilot study on HbA1c variability and CGM indexes, and showed that SD HbA1c is associated with the hypoglycemic indexes of TBR and LBG1. Although the association between HbA1c and CGM indexes has been analyzed previously, this is the first study that dissected the association between HbA1c variability and CGM indexes. HbA1c variability is known to be associated with mortality due to vascular complications in diabetes patients [13], and hypoglycemia is considered a possible contributory factor.

Variations in blood glucose levels are known to be involved in the progression of diabetes vasculopathies, and several studies reported the association of fasting blood glucose variability and postprandial blood glucose with vascular complications.

HbA1c variability has also attracted attention in recent years, with SD and CV used as scales of HbA1c variability. Bouchi et al. [11] reported that SD HbA1c, which is independent of the common cardiovascular risk factors, is associated with the risk of onset of cardiovascular disease (CVD) in T2DM patients. Hirakawa et al. [12] reported that high SD HbA1c is associated with increased risk of onset of vascular events and increased mortality rate in patients of the ADVANCE trial intensive therapy group. Furthermore, Orsi et al. [13] reported that HbA1c variability in T2DM patients is a strong independent predictor of all-cause mortality in T2DM. Although these reports have shown that HbA1c variability is associated with mortality due to diabetes vasculopathies, the significance of HbA1c variability remains unknown. This study is the first to show that HbA1c variability is associated with CGM-based hypoglycemic indexes. Since HbA1c variability reflects the risk of hypoglycemia, it is possible that HbA1c variability is associated with diabetic vascular complications and the related mortality risk.

The objective of glycemic control is to normalize blood glucose level. The United Kingdom Prospective Diabetes Study (UKPDS) [16] obtained data that confirmed the so-called legacy effect associated with intensive glycemic control; therefore, if that state can be maintained, then a long-term prognosis can be expected. On the other hand, intensive glycemic control also increases the risk of hypoglycemia. Particularly severe hypoglycemia must be avoided, as it is associated with poor prognosis. HbA1c is a

useful index for evaluating hyperglycemia; however, since HbA1c cannot be used to evaluate hypoglycemia, it is recommended to set a lower limit blood glucose for HbA1c according to the conditions and risk of hypoglycemia [17, 18]. Our study showed that high HbA1c variability increases the risk of hypoglycemia, and provided the cutoff value for SD HbA1c, above which the risk of hypoglycemia is increased. Our results call for evaluation of hypoglycemia in patients with high SD HbA1c.

As mentioned previously [3, 5], correction of HbA1c is required in order to prevent microangiopathies. In agreement with previous studies, our results showed that the mean HbA1c was associated with the CGM indexes of TIR [19], average glucose [6] and GMI [14]. Although the mean HbA1c was also associated with hyperglycemic indexes, such as maximum, TAR and HBGI, it was not associated with markers of hypoglycemia risk. It is not possible to determine the presence of hypoglycemia by HbA1c values alone; therefore, HbA1c target values should be set individually, taking into consideration the risk of hypoglycemia and support systems.

There were two limitations to this study. The first is we were unable to measure glucose density of  $\geq 500$  mg/dL in FGM; therefore, as per the decision of the primary physician, patients within the FGM range were recruited for this study. As such, our study did not include patients with poor glycemic control, and thus the results of such patients may be different to those obtained in this study. The second limitation is this was a cross-sectional study conducted at two facilities, and included a relatively small number of patients. Consequently, we were unable to examine the effect of each anti-diabetes agent on SD HbA1c. We need to proactively continue with our research on a larger scale in order to substantiate the results of this study.

## Conclusions

We reported for the first time in this study that HbA1c variability is associated with the risk of hypoglycemia (as determined by CGM indexes). It has been reported that HbA1c variability is associated with vascular complications and mortality risk, and hypoglycemia is suggested as a possible contributory factor. For patients with high HbA1c variability, we recommend evaluation of hypoglycemia and adjustment of their treatment regimen, including their glucose-lowering agents.

## List Of Abbreviations

CGM, Continuous Glucose Monitoring;

FGM, Flash Glucose Monitoring;

TIR, the time in range;

T2DM, type 2 diabetes mellitus;

AG, average glucose level;

SD, standard deviation;

CV, coefficient of variation;

TAR, time above range;

TBR, time below range;

GMI, glucose management indicator;

MODD, mean daily difference of blood glucose;

LBGI, low blood glucose index;

HBGI, high blood glucose index;

eGFR, estimated glomerular filtration rate;

AUC, area under the curve;

BMI, Body Mass Index;

DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor;

95%CI, 95% Confidence Interval;

CVD, cardiovascular disease;

## **Declarations**

### **Ethics approval and consent to participate**

The study protocol and opt-out method of informed consent were approved by the ethics committee of the University of Occupational and Environmental Health (Trial registration: H27-186, Registered 25 Dec 2015).

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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## Authors' contributions

AT collected the data. KT and AT analyzed the data. AT wrote the manuscript. YO and KT designed the study and reviewed the manuscript. YT reviewed the manuscript.

All authors read and approved the final manuscript.

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