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Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes

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ABSTRACT

Introduction Preventing the development and progression of diabetic microvascular complications through optimal blood glucose control remains an important challenge. Whether metrics based on continuous glucose monitoring are useful for the management of diabetic microvascular complications is not entirely clear.

Research design and methods This is an exploratory analysis of an ongoing prospective, multicenter, 5-year follow-up observational study. Study participants included 999 outpatients with type 2 diabetes who underwent continuous glucose monitoring at baseline. Associations between continuous glucose monitoring-derived metrics and the severity of diabetic retinopathy or albuminuria were investigated using multivariable proportional odds models.

Results The overall prevalence of diabetic retinopathy was 22.2%. Multivariate analysis with proportional odds models demonstrated that continuous glucose monitoring-derived metrics related to intraday and interday glucose variability are significantly associated with the severity of diabetic retinopathy, even after adjusting for various possible risk factors. However, significant relationships were not observed after adjusting for hemoglobin A1c (HbA1c) levels. The prevalence of microalbuminuria and macroalbuminuria was 20.3% and 6.7%, respectively. Similarly, multivariate analysis demonstrated that those metrics are significantly associated with the severity of albuminuria. These relationships remained significant even after further adjusting for HbA1c levels.

Conclusions Continuous glucose monitoring-derived metrics related to intraday and interday glucose variability are significantly associated with the severity of diabetic retinopathy or albuminuria in patients with type 2 diabetes. Thus, evaluating these metrics might possibly be useful for risk assessment of diabetic microvascular complications.

Trial registration number UMIN000032325.

Significance of this study

What is already known about this subject?

- Recent cross-sectional studies have demonstrated that SD and time in range are each significantly associated with the presence of diabetes retinopathy in inpatients with type 2 diabetes.
- Another study showed that time in range might be associated with the presence of albuminuria in patients with type 2 diabetes, but this association was not statistically significant after adjusting for hemoglobin A1c (HbA1c) levels.

What are the new findings?

- We demonstrated that most FreeStyle Libre Pro continuous glucose monitoring-derived metrics related to intraday and interday glucose variability are significantly associated with the severity of diabetic retinopathy or albuminuria, even after adjusting for various risk factors.
- Notably, these metrics remain predictive factors for the severity of albuminuria after adjusting for HbA1c levels.

How might these results change the focus of research or clinical practice?

- Continuous glucose monitoring-derived metrics could provide medical professionals with information that is useful for assessing the risk of severe diabetic microvascular complications.
- Continuous glucose monitoring-derived metrics might identify treatment targets in addition to those based on HbA1c.

INTRODUCTION

Diabetic retinopathy (DR) is a main cause of visual impairment and blindness.[1] Diabetic nephropathy (DN) is the main cause of end-stage renal disease.[2] Accordingly, taking preventive measures against the development and progression of diabetic microvascular complications in patients with type 2 diabetes is an important task necessary for maintaining daily quality of life, extending healthy lifespan, and reducing healthcare costs. Given that the main cause of microvascular complications is damage to tissues and organs

caused by persistent hyperglycemia,[3] optimal glycemic control is the best way to prevent the development and progression of microvascular complications.

Hemoglobin A1c (HbA1c) is recognized as a gold standard for assessment of glycemic management. Several studies have demonstrated strong associations between HbA1c levels and diabetic microvascular complications.[4 5] In addition, previous studies have indicated that improvement in HbA1c levels is associated with risk reduction in the incidence and progression of diabetic complications in patients with type 2 diabetes.[6 7] Based on these data, current guidelines recommend a target HbA1c level of 7% or less.[8 9] On the other hand, another study failed to show glycemic control to HbA1c <7% has a beneficial effect on the prevention of microvascular complications.[10] One possible explanation for the discrepant findings may be that frequent episodes of severe hypoglycemia counterbalanced the beneficial effects of glycemic control.[11] This hypothesis is based on the fact that HbA1c reflects average glucose over the last few months, but it provides no information on intraday and interday glucose variability and hypoglycemia, both of which may play an important role in the development of macrovascular and microvascular complications.[11–13] In addition, HbA1c has another limitation. HbA1c is affected by factors such as anemia, hemoglobinopathy, chronic kidney disease, and ethnicity.[14] Thus, new metrics reflecting various aspects of glycemic status are needed for the management of diabetic microvascular complications.

Continuous glucose monitoring (CGM) has emerged as an optimal method to obtain a more comprehensive glycemic profile, including data on intraday and interday glucose variability and patterns of hyperglycemia and hypoglycemia. In particular, the Advanced Technologies and Treatments for Diabetes (ATTD) Congress recommends using 10 core CGM metrics that may be most useful in clinical practice.[15] The CGM metrics include three key CGM measurements: (1) time in range (TIR), defined as the percentage of the time spent within the target glucose range; (2) time below range (TBR); and (3) time above range (TAR).[15] These new metrics assessed with CGM could help improve clinical management by providing more information than HbA1c.

Nevertheless, until now, only limited data from cross-sectional studies investigating the relationship between CGM metrics and diabetic microvascular complications have been available. Intriguingly, two recent cross-sectional studies conducted by the same group demonstrated that SD and TIR are each significantly associated with the presence of DR in inpatients with type 2 diabetes.[16 17] Another study showed that TIR is associated with the presence of albuminuria in patients with type 2 diabetes, but this relationship did not reach statistical significance after adjusting for HbA1c levels.[18] On the other hand, a small retrospective cross-sectional study demonstrated that TAR is associated with the presence of DR, but other metrics of glucose variability were not associated with the presence of DR or DN in inpatients with type 2 diabetes.[19] Thus, the association between metrics from CGM and the presence or severity of diabetic microvascular complications in patients with type 2 diabetes has not been fully elucidated yet.

In this exploratory cross-sectional study, we investigated the relationship between CGM-derived metrics and the severity of DR and albuminuria in 999 outpatients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study design

This study is an exploratory subanalysis of an ongoing, observational, prospective cohort study that aims to investigate the relationships between glucose fluctuations evaluated with CGM and the incidence of composite cardiovascular events over a 5-year follow-up period as described previously.[20] This study used baseline study from the cohort study. This study has been registered in the University Hospital Medical Information Network Clinical Trials Registry, which is a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors.

Study population

The study population consists of Japanese patients with type 2 diabetes who regularly attend the outpatient diabetes clinics of 34 institutions across Japan (with investigator names in parentheses shown in online supplemental table 1). The inclusion criteria were as follows: (1) age ≥30 years and ≤80 years, regardless of gender; (2) receiving treatment for type 2 diabetes at one of the participating outpatient clinics; (3) informed consent for study participation; (4) no changes (including new prescriptions) in antidiabetic medications for 6 months before written informed consent was obtained (insulin dosage changes were allowed); and (5) no anticipated changes in antidiabetic medications from the time of enrollment until a CGM device was applied on the back of the upper arm (insulin dosage changes were allowed). The following exclusion criteria were also applied: (1) type 1 or secondary diabetes; (2) presence of severe infectious disease preoperatively, postoperatively, or associated with severe trauma; (3) history of myocardial infarction, angina pectoris, cerebral stroke, cerebral infarction, or arteriosclerosis obliterans; (4) current treatment with artificial dialysis; (5) moderate liver dysfunction defined as aspartate aminotransferase ≥100 IU/L; (6) moderate or severe heart failure (New York Heart Association stage III or worse); (7) pregnancy, lactation, possible pregnancy, or plans to become pregnant during the study period; (8) present or history of a malignant tumor; (9) use of a sensor-augmented insulin pump; (10) type 2 diabetes diagnosis within the past year; and (11) judged as ineligible by the clinical investigators. Patients not currently receiving medication for a malignant tumor, with no disease recurrence to date, and without recurrence risks during the study period were allowed to participate.

Consecutive subjects were screened. Patients who meet the eligibility criteria were asked to participate in the present study. A total of 1000 patients who met the eligibility criteria were recruited between May 2018 and March 2019. One patient withdrew consent. Written informed consent was obtained from all participants after a full explanation of the study.

Biochemical tests

Blood samples were obtained at visits after overnight fasting. Renal function tests, lipid levels, and HbA1c (National Glycohemoglobin Standardization Program) were measured with standard techniques. Urinary albumin excretion (UAE) was measured using a latex agglutination assay on a spot urine sample. Estimated glomerular filtration rate (eGFR) was calculated using a formula.[21]

DR and DN assessment

The presence and severity of DR were determined by trained ophthalmologists. The patients were grouped into four groups based on medical records: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), preproliferative diabetic retinopathy (PPDR), or proliferative diabetic retinopathy (PDR). DN was defined according to the level of UAE: <30 mg/g creatinine was defined as normoalbuminuria, 30–299 mg/g creatinine was defined as microalbuminuria, and ≥300 mg/g creatinine was defined as macroalbuminuria.

CGM with the FreeStyle Libre Pro device

The FreeStyle Libre Pro (Abbott Japan, Tokyo, Japan) CGM (FLP-CGM) device, which measures glucose levels every 15 min for up to 14 days, was used in this study as previously reported.[20] Other than wearing FLP-CGM, there were no restrictions on participants' daily lives. Downloaded data sets were further analyzed. Glucose variability was assessed based on mean amplitude of glycemic excursion (MAGE),[22] SD, and glucose coefficient of variation (CV). MAGE was calculated as the arithmetic mean of the differences between consecutive peaks and nadirs, provided that the differences are greater than 1 SD of the mean glucose value. CV (%) was calculated by dividing SD by the mean of the corresponding glucose readings. The original statistical analysis plan (SAP) for this study was reported in the initial study protocol.[20] We added some CGM-derived metrics in this study since the ATTD Congress proposed some CGM-derived metrics as useful clinical targets that complement HbA1c.[15] Thus, we updated the SAP prior to database lock. Mean glucose was measured from data collected during FLP-CGM. TIR was defined as the percentage of the time spent in the target range between 3.9 and 10.0 mmol/L ($TIR^{3.9–10\ mmol/L}$), time above target glucose range ($TAR^{>10\ mmol/L}$, $TAR^{>13.9\ mmol/L}$), and time below target glucose range ($TBR^{<3.9\ mmol/L}$, $TBR^{<3.0\ mmol/L}$). Low blood glucose index (LBGI) and high blood glucose index (HBGI) formulae were implemented by converting glucose values into risk scores.[23] In addition, mean of daily differences (MODD)[24] in glucose levels and IQR were calculated to assess interday glucose variability. MODD was calculated as the mean of the absolute difference between glucose levels measured at the same time on 2 consecutive days. IQR was calculated using values from the same time of day during the monitoring period. Since a previous study demonstrated that FLP-CGM was less accurate during the first 24 hours (from the first day to the second day) after insertion and during the last 4 days of its 14-day lifetime,[25] we analyzed FLP-CGM data over the middle 8-day period.

Statistical analysis

Results are presented as mean±SD for continuous variables or number (proportion) of patients for categorical variables. Several parameters were logarithmically transformed to approximate the normal distribution. Continuous data were compared using analysis of variance, and categorical data were compared using χ^2 test or Fisher's exact test as appropriate. Multivariate analysis with proportional odds models was performed to investigate whether FLP-CGM-derived metrics are associated with the severity of diabetic microvascular complications. Conventional possible risk factors evaluated by clinical, biochemical, and metabolic tests based on clinical judgment were included in the models. All statistical tests were two-sided with a 5% significance level. All analyses were performed using SAS software V.9.4 or above.

RESULTS

Relationship between FLP-CGM-derived metrics and DR severity

The baseline clinical characteristics of the 999 patients with type 2 diabetes are summarized in table 1. The mean age was 64.6±9.6 years, 60.9% were male, the mean HbA1c was 7.1%±0.8% (53.7±8.8 mmol/mol), and the estimated duration of type 2 diabetes was 12.9±8.5 years.

In this study, 222 of 999 (22.2%) were diagnosed as having DR. Subject characteristics by DR stage are presented in table 2. SDR was observed in 133 subjects (13.3%), PPDR in 50 (5.0%), and PDR in 39 (3.9%). Subjects with more severe DR were more likely to be older, have longer duration of diabetes mellitus, higher HbA1c levels, higher uric acid levels, higher UAE, and lower eGFR. All FLP-CGM-derived metrics except $TBR^{<3.9\ mmol/L}$ and $TBR^{<3.0\ mmol/L}$ were significantly different among the groups. Subjects with more severe DR were more likely to be treated with oral antidiabetic drugs and antihypertensive drugs, respectively.

Next, we investigated the relationship between FLP-CGM-derived metrics and DR severity in patients with type 2 diabetes. In a proportional odds model with the patients with NDR as the reference group, HbA1c and FLP-CGM-derived metrics except for CV, $TBR^{<3.9\ mmol/L}$, $TBR^{<3.0\ mmol/L}$, and LBGI were significantly associated with DR severity (model 1 in table 3). In models 2 and 3, the associations remained significant after adjusting

Table 1 Patient demographic and background characteristics

Parameter	
Age (years)	64.6±9.6 (n=999)
Male gender (%)	608 (60.9)
BMI (kg/m^2)	24.6±3.9 (n=999)
Estimated duration of diabetes (years)	12.9±8.5 (n=999)
Systolic blood pressure (mm Hg)	131.2±14.8 (n=999)
Diastolic blood pressure (mm Hg)	75.5±11.0 (n=999)
HbA1c (%)	7.1±0.8 (n=999)
HbA1c (mmol/mol)	53.7±8.8 (n=999)
Total cholesterol (mmol/L)	4.81±0.82 (n=964)
LDL cholesterol (mmol/L)	2.67±0.69 (n=990)
HDL cholesterol (mmol/L)	1.56±0.41 (n=998)
Triglycerides (mmol/L)	1.4±0.9(n=999)
Uric acid (µmol/L)	307.4±73.0 (n=994)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	73.4±20.6 (n=999)
Use of oral glucose-lowering agents (%)	894 (89.5)
Metformin (%)	543 (54.4)
Sulfonylureas (%)	127 (12.7)
Glinides (%)	68 (6.8)
Dipeptidyl peptidase-4 inhibitors (%)	577 (57.8)
Sodium-glucose cotransporter-2 inhibitors (%)	231 (23.1)
Thiazolidinediones (%)	143 (14.3)
α-glucosidase inhibitors (%)	172 (17.2)
Glucagon-like peptide-1 antagonists (%)	74 (7.4)
Insulin (%)	158 (15.8)
Use of antihypertensive drugs	483 (48.3)
ACE inhibitors (%)	28 (2.8)
Angiotensin II receptor blockers (%)	390 (39.0)
Calcium channel blockers (%)	273 (27.3)
Diuretic drugs (%)	57 (5.7)
α-adrenergic receptor antagonists (%)	19 (1.9)
β-adrenergic receptor antagonists (%)	33 (3.3)
Use of lipid-lowering agents (%)	595 (59.7)
Statins (%)	508 (51.0)
Ezetimibe (%)	107 (10.7)
Fibrates (%)	41 (4.1)
Use of antithrombotic agents (%)	64 (6.4)
Antiplatelet agents (%)	50 (5.0)
Anticoagulants (%)	15 (1.5)
FLP-CGM-derived metrics	
Mean glucose (mmol/L)	7.80±1.79 (n=999)
SD (mmol/L)	2.04±0.63 (n=999)
CV (%)	26.2±5.79 (n=999)
MAGE (mmol/L)	5.46±2.00 (n=999)
TIR$^{3.9–10\ mmol/L}$ (%)	78.9±18.6 (n=999)
TAR$^{>10\ mmol/L}$ (%)	19.0±19.2 (n=999)
TAR$^{>13.9\ mmol/L}$ (%)	3.85±9.31 (n=999)
TBR$^{<3.9\ mmol/L}$ (%)	2.16±4.71 (n=999)
TBR$^{<3.0\ mmol/L}$ (%)	0.33±1.53 (n=999)
LBGI	1.56±1.67 (n=999)
HBGI	5.58±4.64 (n=999)
MODD (mmol/L)	1.73±0.64 (n=999)
IQR (mmol/L)	2.14±0.81 (n=999)

Data are mean±SD or number of patients (%).
BMI, body mass index; CV, coefficient of variation; FLP-CGM, FreeStyle Libre Pro continuous glucose monitoring device; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HDL, high-density lipoprotein; LBGI, low blood glucose index; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; TAR, time above range; TBR, time below range; TIR, time in range.

for age, gender, body mass index (BMI), duration of diabetes, systolic blood pressure, lipid parameters, uric acid, eGFR, UAE, smoking, alcohol consumption, use of insulin therapy, use of ACE inhibitors and/or angiotensin II receptor blockers (ARBs), use of statins, and use of antiplatelet agents (table 2). However, we did not find any significant associations between FLP-CGM-derived metrics and DR severity after adjusting for HbA1c in addition to parameters included in model 3 (model 4 in table 3).

Relationship between FLP-CGM-derived metrics and albuminuria severity

Of 999 subjects, 729 (73.0%) were classified as having normoalbuminuria, 203 (20.3%) were classified as having microalbuminuria, and 67 (6.7%) were classified as having macroalbuminuria. The clinical characteristics of the study participants stratified by albuminuria status are summarized in table 4. Subjects with more severe albuminuria were more likely to have longer duration of diabetes mellitus, higher BMI, higher prevalence of DR, higher HbA1c levels, higher triglyceride levels, higher uric acid levels, lower high-density lipoprotein levels, and lower eGFR. Among the groups, there were significant differences in most FLP-CGM-derived metrics, except for

Table 2 Patient demographic and background characteristics by diabetic retinopathy stage

Parameter	NDR (n=777)	SDR (n=133)	PPDR (n=50)	PDR (n=39)	P value
Age (years)	64.1±9.8	65.3±9.6	67.3±8.5	66.6±7.2	0.039
Male gender (%)	482 (62.0)	84 (63.2)	23 (46.0)	19 (48.7)	0.050
BMI (kg/m^2)	24.6±3.8	24.7±3.8	24.4±4.1	25.1±4.3	0.838
Estimated duration of diabetes (years)	11.8±8.0	15.6±8.9	17.5±9.6	19.1±9.6	<0.001
Systolic blood pressure (mm Hg)	130.9±15.1	133.1±14.0	132.3±13.9	130.3±14.4	0.403
Diastolic blood pressure (mm Hg)	75.6±11.3	76.5±10.2	71.9±9.7	75.5±10.4	0.089
HbA1c (%)	7.0±0.8	7.2±0.9	7.6±0.9	7.6±1.1	<0.001
HbA1c (mmol/mol)	52.8±8.2	55.2±9.4	59.1±9.6	59.8±11.8	<0.001
Total cholesterol (mmol/L)	4.87±0.81	4.55±0.79	4.51±0.63	4.81±0.96	<0.001
LDL cholesterol (mmol/L)	2.71±0.68	2.54±0.67	2.45±0.78	2.57±0.65	0.005
HDL cholesterol (mmol/L)	1.57±0.41	1.51±0.33	1.57±0.37	1.57±0.49	0.450
Triglycerides (mmol/L)	1.4±0.9	1.1±0.6	1.5±1.2	1.5±1.0	0.029
Uric acid (µmol/L)	306.6±72.3	315.4±72.7	278.1±71.3	333.9±78.1	0.002
Estimated glomerular filtration rate (mL/min/1.73 m^2)	75±20	72±24	68±18	58±25	<0.001
Urinary albumin excretion (mg/g creatinine)	67.9±254	73.6±206	212±464	607±1261	<0.001
Use of oral glucose-lowering agents	677 (87.1)	129 (97)	49 (98)	39 (100)	<0.001
Metformin (%)	402 (51.7)	93 (69.9)	34 (68.0)	14 (35.9)	<0.001
Sulfonylureas (%)	89 (11.5)	20 (15.0)	8 (16.0)	10 (25.6)	0.044
Glinides (%)	40 (5.1)	12 (9.0)	9 (18.0)	7 (17.9)	<0.001
Dipeptidyl peptidase-4 inhibitors (%)	435 (56.0)	87 (65.4)	31 (62.0)	24 (61.5)	0.188
Sodium-glucose cotransporter-2 inhibitors (%)	167 (21.5)	34 (25.6)	19 (38.0)	11 (28.2)	0.038
Thiazolidinediones (%)	100 (12.9)	23 (17.3)	13 (26.0)	7 (17.9)	0.041
α-glucosidase inhibitors (%)	117 (15.1)	39 (29.3)	10 (20.0)	6 (15.4)	<0.001
Glucagon-like peptide-1 receptor agonists (%)	36 (4.6)	18 (13.5)	11 (22.0)	9 (23.1)	<0.001
Insulin (%)	94 (12.1)	31 (23.3)	13 (26.0)	20 (51.3)	<0.001
Use of antihypertensive drugs	346 (44.5)	79 (59.4)	29 (58.0)	29 (74.4)	<0.001
ACE inhibitors (%)	19 (2.4)	5 (3.8)	2 (4.0)	2 (5.1)	0.323
Angiotensin II receptor blockers (%)	278 (35.8)	67 (50.4)	22 (44.0)	23 (59.0)	<0.001
Calcium channel blockers (%)	193 (24.8)	44 (33.1)	19 (38.0)	17 (43.6)	0.005
Diuretic drugs (%)	35 (4.5)	13 (9.8)	3 (6.0)	6 (15.4)	0.006
α-adrenergic receptor antagonists (%)	13 (1.7)	4 (3.0)	1 (2.0)	1 (2.6)	0.455
β-adrenergic receptor antagonists (%)	26 (3.3)	4 (3.0)	1 (2.0)	2 (5.1)	1.000
Use of lipid-lowering agents (%)	450 (58.1)	93 (69.9)	35 (70.0)	17 (43.6)	0.005
Statins (%)	386 (49.8)	73 (54.9)	32 (64.0)	17 (43.6)	0.140
Ezetimibe (%)	76 (9.8)	23 (17.3)	5 (10.0)	3 (7.7)	0.089
Fibrates (%)	31 (4)	6 (4.5)	4 (8.0)	0 (0.0)	0.298
Use of antithrombotic agents (%)	48 (6.2)	8 (6.0)	5 (10.0)	3 (7.7)	0.623
Antiplatelet agents (%)	36 (4.6)	8 (6.0)	5 (10.0)	1 (2.6)	0.297
Anticoagulants (%)	13 (1.7)	0 (0.0)	0 (0.0)	2 (5.1)	0.110
FLP-CGM-derived metrics					
Mean glucose (mmol/L)	7.66±1.71	8.09±1.77	8.55±2.06	8.61±2.48	<0.001
SD (mmol/L)	2.00±0.60	2.07±0.61	2.20±0.72	2.46±0.80	<0.001
CV (%)	26.2±5.84	25.5±5.38	25.9±5.72	28.8±5.66	0.019
MAGE (mmol/L)	5.36±1.93	5.43±1.76	5.93±2.39	6.82±2.99	<0.001

Continued

Table 2 Continued

Parameter	NDR (n=777)	SDR (n=133)	PPDR (n=50)	PDR (n=39)	P value
$TIR^{3.9–10\ mmol/L}$ (%)	80.4±17.6	76.3±19.8	70.3±22.8	68.9±21.9	<0.001
$TAR^{>10\ mmol/L}$ (%)	17.4±18.0	22.2±20.7	27.6±24.5	27.8±22.8	<0.001
$TAR^{>13.9\ mmol/L}$ (%)	3.28±8.64	4.41±9.20	7.55±10.9	8.51±16.0	<0.001
$TBR^{<3.9\ mmol/L}$ (%)	2.21±4.93	1.56±3.33	2.08±4.28	3.29±4.72	0.210
$TBR^{<3.0\ mmol/L}$ (%)	0.350±1.67	0.11±0.36	0.27±0.77	0.68±1.59	0.178
LBGI	1.60±1.72	1.25±1.20	1.31±1.44	2.16±1.99	0.010
HBGI	5.26±4.35	5.99±4.50	7.26±5.29	8.38±7.58	<0.001
MODD (mmol/L)	1.69±0.61	1.78±0.56	1.95±0.66	2.34±1.00	<0.001
IQR (mmol/L)	2.09±0.79	2.16±0.72	2.33±0.76	2.95±1.20	<0.001

Data are mean±SD or number of patients (%).
Continuous data were compared using analysis of variance. Categorical data were compared using χ^2 test or Fisher's exact test as appropriate.
BMI, body mass index; CV, coefficient of variation; FLP-CGM, FreeStyle Libre Pro continuous glucose monitoring device; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HDL, high-density lipoprotein; LBGI, low blood glucose index; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; SDR, simple retinopathy; TAR, time above range; TBR, time below range; TIR, time in range.

CV, $TBR^{<3.9\ mmol/L}$, $TBR^{<3.0\ mmol/L}$, and LBGI. Subjects with more severe albuminuria were more likely to be treated with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin, as well as antihypertensive drugs such as calcium channel blockers, ACE inhibitors, and ARBs.

Next, we investigated the relationship between FLP-CGM-derived metrics and albuminuria severity. In a proportional odds model with the patients with normoalbuminuria as the reference group, most FLP-CGM-derived metrics except for CV, $TBR^{<3.9\ mmol/L}$, $TBR^{<3.0\ mmol/L}$, and LBGI were significantly associated with albuminuria severity (model 1), as shown in table 5. In models 2 and 3, most FLP-CGM-derived metrics, except for CV, $TBR^{<3.9\ mmol/L}$, $TBR^{<3.0\ mmol/L}$, and LBGI were significantly associated with albuminuria severity after adjusting for age, gender, BMI, duration of diabetes, systolic blood pressure, lipid parameters, uric acid, eGFR, smoking, alcohol consumption, use of insulin therapy, use of ACE inhibitors and/or ARBs, use of statins, use of antiplatelet agents, and presence of DR. Associations between FLP-CGM-derived metrics and albuminuria severity remained significant after adjusting for HbA1c and parameters included in model 3 (model 4 in table 5). We performed multiple linear regression with logarithmic-transformed UAE as the dependent variable to further examine the association between UAE and CGM-derived metrics. Similar findings were obtained (data not shown). Thus, these metrics are predictive factors for the severity of albuminuria independent of HbA1c levels.

DISCUSSION

In this study, we demonstrated that most FLP-CGM-derived metrics related to intraday and interday glucose variability are significantly associated with the severity of DR or albuminuria, even after adjusting for various risk factors in 999 outpatients with type 2 diabetes. Notably, these metrics remain predictive factors for determining the severity of albuminuria after adjusting for HbA1c levels.

A pooled subanalysis of population-based studies demonstrated that the prevalence of any DR in patients with diabetes during 2000–2008 was substantially lower than the prevalence observed before 2000.[26] The relative reduction in the prevalence of any DR from 49.6% to 24.8% may reflect improvements in medical care and management of diabetes and DR-related risk factors, including blood pressure, as well as early disease identification and medical provider awareness. In that study,[26] the prevalence of any DR and PDR in patients with type 2 diabetes during 1980–2008 was 27.2% and 2.6%, respectively. Our study demonstrated that the prevalence of any DR was 22.2% and PDR was 3.9%. Given that risk factors for DR such as blood glucose and blood pressure were relatively well controlled in our study, the prevalence of DR in our study is reasonable.

The Japan Diabetes Complications Study demonstrated that HbA1c is the strongest risk factor for development and progression of DR, while longer duration of diabetes, systolic blood pressure, and BMI are positively associated with incident DR.[27] In fact, previous studies have demonstrated that improvement in HbA1c levels is associated with reduced risk of DR development and progression in patients with type 2 diabetes.[6 7] In accordance with those findings, our study indicated that HbA1c is positively associated with DR severity, even after adjusting for several risk factors. On the other hand, a recent study demonstrated that $TIR^{3.9–10\ mmol/L}$ based on

Table 3 Associations between FLP-CGM-derived metrics and diabetic retinopathy severity

Parameter	OR (95% CI)	P value
Mean glucose (1 mmol/L increase)		
Model 1	1.21 (1.12 to 1.30)	<0.001
Model 2	1.20 (1.10 to 1.29)	<0.001
Model 3	1.22 (1.11 to 1.33)	<0.001
Model 4	1.07 (0.94 to 1.22)	0.311
SD (mmol/L) (1 mmol/L increase)		
Model 1	1.57 (1.26 to 1.96)	<0.001
Model 2	1.36 (1.08 to 1.71)	0.010
Model 3	1.30 (1.00 to 1.69)	0.049
Model 4	0.97 (0.72 to 1.31)	0.842
CV (%) (1% increase)		
Model 1	1.00 (0.98 to 1.03)	0.747
Model 2	0.99 (0.96 to 1.01)	0.365
Model 3	0.98 (0.95 to 1.00)	0.089
Model 4	0.98 (0.95 to 1.01)	0.170
MAGE (1 mmol/L increase)		
Model 1	1.13 (1.05 to 1.21)	<0.001
Model 2	1.10 (1.03 to 1.18)	0.007
Model 3	1.10 (1.02 to 1.19)	0.015
Model 4	1.03 (0.94 to 1.12)	0.531
$TIR^{3.9–10\ mmol/L}$ (10% increase)		
Model 1	0.83 (0.77 to 0.89)	<0.001
Model 2	0.85 (0.79 to 0.91)	<0.001
Model 3	0.85 (0.78 to 0.93)	<0.001
Model 4	0.97 (0.86 to 1.09)	0.616
$TAR^{>10\ mmol/L}$ (1% increase)		
Model 1	1.02 (1.01 to 1.04)	<0.001
Model 2	1.02 (1.01 to 1.02)	<0.001
Model 3	1.02 (1.01 to 1.03)	<0.001
Model 4	1.01 (0.99 to 1.02)	0.371
$TAR^{>13.9\ mmol/L}$ (1% increase)		
Model 1	1.03 (1.01 to 1.04)	<0.001
Model 2	1.03 (1.01 to 1.04)	<0.001
Model 3	1.03 (1.01 to 1.05)	<0.001
Model 4	1.01 (0.99 to 1.03)	0.541
$TBR^{<3.9\ mmol/L}$ (1% increase)		
Model 1	0.99 (0.96 to 1.03)	0.677
Model 2	0.99 (0.95 to 1.02)	0.397
Model 3	0.96 (0.93 to 0.99)	0.028
Model 4	0.98 (0.94 to 1.01)	0.238
$TBR^{<3.0\ mmol/L}$ (1% increase)		
Model 1	0.96 (0.85 to 1.08)	0.499
Model 2	0.94 (0.83 to 1.06)	0.288
Model 3	0.84 (0.72 to 0.97)	0.020
Model 4	0.88 (0.77 to 1.01)	0.071
LBGI (1-unit increase)		
Model 1	0.95 (0.86 to 1.04)	0.268
Model 2	0.92 (0.84 to 1.02)	0.097
Model 3	0.84 (0.76 to 0.94)	0.002
Model 4	0.91 (0.82 to 1.01)	0.069
HBGI (1-unit increase)		
Model 1	1.07 (1.04 to 1.10)	<0.001
Model 2	1.06 (1.03 to 1.09)	<0.001
Model 3	1.06 (1.03 to 1.10)	<0.001
Model 4	1.01 (0.96 to 1.06)	0.745
MODD (1 mmol/L increase)		
Model 1	1.84 (1.49 to 2.26)	<0.001
Model 2	1.75 (1.41 to 2.18)	<0.001
Model 3	1.67 (1.28 to 2.19)	<0.001
Model 4	1.27 (0.93 to 1.74)	0.126
IQR (1 mmol/L increase)		
Model 1	1.50 (1.28 to 1.77)	<0.001
Model 2	1.48 (1.24 to 1.75)	<0.001
Model 3	1.42 (1.15 to 1.76)	0.001
Model 4	1.11 (0.87 to 1.43)	0.399
HbA1c (1% increase)		
Model 1	1.76 (1.48 to 2.08)	<0.001
Model 2	1.62 (1.35 to 1.94)	<0.001
Model 3	1.66 (1.35 to 2.04)	<0.001

Model 1: crude.
Model 2: adjusted for age, gender, BMI, and duration of diabetes.
Model 3: adjusted for variables in model 2 plus systolic blood pressure, total cholesterol, HDL cholesterol, logarithm of triglycerides, serum uric acid, estimated glomerular filtration rate, logarithm of urinary albumin excretion, smoker, alcohol consumption, use of insulin therapy, use of ACE inhibitors and/or angiotensin II receptor blockers, use of statins, and use of antiplatelet agents.
Model 4: adjusted for variables in model 3 plus HbA1c.
BMI, body mass index; CV, coefficient of variation; FLP-CGM, FreeStyle Libre Pro continuous glucose monitoring; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HDL, high-density lipoprotein; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; TAR, time above range; TBR, time below range; TIR, time in range.

seven-point glucose testing is inversely associated with the risk of DR progression in patients with type 1 diabetes.[28] Similarly, another cross-sectional study demonstrated that CGM-derived $TIR^{3.9–10\ mmol/L}$ is inversely associated with DR severity, independent of HbA1c levels in patients with type 2 diabetes.[17] Our study also demonstrated that FLP-CGM-derived $TIR^{3.9–10.0\ mmol/L}$ is inversely associated with DR severity, even after adjusting for several possible risk factors in patients with type 2 diabetes. However,

Table 4 Patient demographic and background characteristics stratified by albuminuria status

Parameter	Normoalbuminuria (n=729)	Microalbuminuria (n=203)	Macroalbuminuria (n=67)	P value
Age (years)	64.1±9.5	66.2±9.8	64.6±10.0	0.026
Male gender (%)	441 (60.5)	120 (59.1)	47 (70.1)	0.256
BMI (kg/m^2)	24.3±3.9	25.2±3.6	25.9±4.0	<0.001
Estimated duration of diabetes (years)	12.0±8.2	14.6±8.7	17.2±9.4	<0.001
Systolic blood pressure (mm Hg)	130.7±14.7	132.5±14.6	133.4±17.1	0.147
Diastolic blood pressure (mm Hg)	75.5±10.8	74.8±11.7	77.6±11.9	0.198
HbA1c (%)	7.0±0.7	7.3±0.9	7.5±1.1	<0.001
HbA1c (mmol/mol)	52.6±7.8	55.8±10.0	58.5±12.3	<0.001
Total cholesterol (mmol/L)	4.83±0.81	4.76±0.74	4.72±1.05	0.437
LDL cholesterol (mmol/L)	2.69±0.68	2.64±0.64	2.43±0.81	0.010
HDL cholesterol (mmol/L)	1.59±0.41	1.49±0.41	1.49±0.37	0.004
Triglycerides (mmol/L)	1.3±0.8	1.4±0.9	2.0±1.8	<0.001
Uric acid (µmol/L)	300.6±69.9	314.8±79.0	358.7±65.0	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m^2)	76±19	69±21	58±25	<0.001
Diabetic retinopathy (%)	123 (16.9)	63 (31.0)	36 (53.7)	<0.001
Use of oral glucose-lowering agents (%)	639 (88)	188 (93)	67 (100)	0.002
Metformin (%)	387 (53)	120 (59)	36 (54)	0.311
Sulfonylureas (%)	84 (12)	32 (16)	11 (16)	0.177
Glinides (%)	44 (6)	17 (8)	7 (10)	0.238
Dipeptidyl peptidase-4 inhibitors (%)	412 (57)	118 (58)	47 (70)	0.096
Sodium-glucose cotransporter-2 inhibitors (%)	149 (20)	59 (29)	23 (34)	0.003
Thiazolidinediones (%)	99 (14)	30 (15)	14 (21)	0.256
α-glucosidase inhibitors (%)	125 (17)	32 (16)	15 (22)	0.458
Glucagon-like peptide-1 receptor agonists (%)	40 (6)	22 (11)	12 (18)	<0.001
Insulin (%)	92 (13)	44 (22)	22 (33)	<0.001
Use of antihypertensive drugs (%)	298 (41)	130 (64)	55 (82)	<0.001
ACE inhibitors (%)	13 (2)	11 (5)	4 (6)	0.006
Angiotensin II receptor blockers (%)	245 (34)	101 (50)	44 (66)	<0.001
Calcium channel blockers (%)	154 (21)	86 (42)	33 (49)	<0.001
Diuretic drugs (%)	33 (5)	17 (8)	7 (10)	0.025
α-adrenergic receptor antagonists (%)	9 (1)	6 (3)	4 (6)	0.013
β-adrenergic receptor antagonists (%)	15 (2)	12 (6)	6 (9)	<0.001
Use of lipid-lowering agents (%)	426 (59)	121 (60)	48 (72)	0.114
Statins (%)	360 (50)	106 (52)	42 (63)	0.110
Ezetimibe (%)	75 (10)	21 (10)	11 (16)	0.298
Fibrates (%)	29 (4)	9 (4)	3 (5)	0.949
Use of antithrombotic agents (%)	46 (6)	14 (7)	4 (6)	0.948
Antiplatelet agents (%)	36 (5)	11 (5)	3 (5)	0.935
Anticoagulants (%)	11 (2)	3 (2)	1 (2)	1.000
FLP-CGM-derived metrics				
Mean glucose (mmol/L)	7.59±1.59	8.25±1.97	8.70±2.62	<0.001
SD (mmol/L)	1.97±0.58	2.20±0.68	2.29±0.77	<0.001
CV (%)	26.0±5.72	26.8±5.90	26.7±6.11	0.142
MAGE (mmol/L)	5.26±1.85	5.86±2.08	6.34±2.79	<0.001

Continued

Table 4 Continued

Parameter	Normoalbuminuria (n=729)	Microalbuminuria (n=203)	Macroalbuminuria (n=67)	P value
$TIR^{3.9–10\ mmol/L}$ (%)	81.1±17.1	74.3±19.5	68.0±24.7	<0.001
$TAR^{>10\ mmol/L}$ (%)	16.7±17.5	23.8±20.4	28.7±26.3	<0.001
$TAR^{>13.9\ mmol/L}$ (%)	2.87±7.4	5.71±11.8	8.86±15.7	<0.001
$TBR^{<3.9\ mmol/L}$ (%)	2.12±4.58	1.91±4.06	3.35±7.20	0.086
$TBR^{<3.0\ mmol/L}$ (%)	0.33±1.64	0.20±0.77	0.65±1.85	0.117
LBGI	1.58±1.68	1.41±1.44	1.79±2.07	0.226
HBGI	5.04±3.86	6.70±5.48	8.08±7.40	<0.001
MODD (mmol/L)	1.66±0.59	1.88±0.64	2.13±0.90	<0.001
IQR (mmol/L)	2.05±0.76	2.31±0.82	2.65±1.11	<0.001

Data are mean±SD or number of patients (%).
Continuous data were compared using analysis of variance. Categorical data were compared using χ^2 test or Fisher's exact test as appropriate.
BMI, body mass index; CV, coefficient of variation; FLP-CGM, FreeStyle Libre Pro continuous glucose monitoring device; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HDL, high-density lipoprotein; LBGI, low blood glucose index; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; TAR, time above range; TBR, time below range; TIR, time in range.

associations between $TIR^{3.9–10\ mmol/L}$ as well as other FLP-CGM-derived metrics including SD, MAGE, $TAR^{>10\ mmol/L}$, $TAR^{>13.9\ mmol/L}$, HBGI, MODD, and IQR and DR severity did not reach statistical significance after adjusting for HbA1c levels.

A possible explanation for the discrepant findings may be differences in characteristics of patients between our studies and the other two previous studies. First, the subjects of a prior study[28] were patients with type 1 diabetes treated with insulin, which is completely different from our subjects. In addition, $TIR^{3.9–10mmol/L}$ derived from seven-point blood glucose testing reflects one-daytime values; it does not reflect the overnight period and has limited ability to assess intraday and interglycemicinterday glucose variability. The subjects of the other prior study[17] were hospitalized for the treatment of diabetes. They were mainly treated with insulin and had hospital meals during a few days of CGM measurement. Thus, these patients are anticipated to have lower $TIR^{3.9–10mmol/L}$ despite substantially higher HbA1c levels. Accordingly, that data may not be generalizable to outpatients with type 2 diabetes under their usual living conditions.

Recently, SGLT-2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and GLP-1 receptor agonists have been frequently used for patients with type 2 diabetes. These drugs are reported to decrease glucose fluctuations without increasing the risk of hypoglycemia.[29] Not surprisingly, our subjects had lower HbA1c levels and were more likely to have lower SD and MAGE and higher $TIR^{3.9–10mmol/L}$, because a higher proportion used DPP-4 inhibitors and SGLT-2 inhibitors than those in a previous study.[29] Thus, it could be difficult to detect the impact of glycemic variability on DR severity independent of HbA1c levels in our study subjects. However, it should be noted that FLP-CGM-derived metrics related to intraday and interday glucose variability were still significantly associated with DR severity after adjusting for possible risk factors other than HbA1c. These findings highlight the substantial role of intraday and interday glucose variability in the pathogenesis of DR. Although FLP-CGM-derived metrics are unlikely to be more useful than HbA1c in terms of predicting DR severity, HbA1c alone might not provide information on intraday and interday glucose variability. Accordingly, our data suggest FLP-CGM-derived metrics might be important complements to HbA1c.

According to serial cross-sectional studies of patients with diabetes who participated in the National Health and Nutrition Examination Surveys, the prevalence of albuminuria declined progressively from 20.8% in 1988–1994 to 15.9% in 2009–2014.[30] Higher prevalence of treatment with antidiabetic agents, renin–angiotensin system inhibitors, and statins may account for the reduction in the prevalence of albuminuria. On the other hand, an in vitro study showed that intermittent treatment of high blood glucose levels increases apoptosis of mesangial cells by increasing levels of inflammatory cytokines and oxidative stress, leading to the development of DN.[31] However, there are limited data about the clinical impact of intraday and interday glucose variability on the presence or progression of albuminuria in patients with type 2 diabetes. Two previous studies conducted by the same group did not show a significant association between CGM-derived metrics of intraday and interday glucose variability and the presence of albuminuria independent of HbA1c levels in patients with type 2 diabetes with HbA1c levels of more than 8%.[32 33] In contrast, our study clearly showed close relationships between FLP-CGM-derived metrics related to intraday and interday glucose variability and the severity of albuminuria,

Table 5 Associations between FLP-CGM-derived metrics and albuminuria severity

Parameter	OR (95% CI)	P value
Mean glucose (1 mmol/L increase)		
Model 1	1.26 (1.17 to 1.35)	<0.001
Model 2	1.24 (1.15 to 1.34)	<0.001
Model 3	1.24 (1.14 to 1.36)	<0.001
Model 4	1.28 (1.14 to 1.45)	<0.001
SD (1 mmol/L increase)		
Model 1	1.86 (1.50 to 2.31)	<0.001
Model 2	1.81 (1.45 to 2.27)	<0.001
Model 3	1.72 (1.33 to 2.21)	<0.001
Model 4	1.57 (1.18 to 2.08)	0.002
CV (1% increase)		
Model 1	1.02 (1.00 to 1.05)	0.053
Model 2	1.02 (1.00 to 1.05)	0.066
Model 3	1.02 (0.99 to 1.04)	0.288
Model 4	1.02 (0.99 to 1.05)	0.251
MAGE (1 mmol/L increase)		
Model 1	1.20 (1.12 to 1.28)	<0.001
Model 2	1.19 (1.11 to 1.27)	<0.001
Model 3	1.17 (1.09 to 1.26)	<0.001
Model 4	1.14 (1.05 to 1.24)	0.001
$TIR^{3.9–10\ mmol/L}$ (10% increase)		
Model 1	0.97 (0.74 to 0.85)	<0.001
Model 2	0.80 (0.75 to 0.86)	<0.001
Model 3	0.81 (0.75 to 0.89)	<0.001
Model 4	0.81 (0.72 to 0.90)	<0.001
$TAR^{>10\ mmol/L}$ (1% increase)		
Model 1	1.02 (1.02 to 1.03)	<0.001
Model 2	1.02 (1.01 to 1.03)	<0.001
Model 3	1.02 (1.01 to 1.03)	<0.001
Model 4	1.02 (1.01 to 1.03)	<0.001
$TAR^{>13.9\ mmol/L}$ (1% increase)		
Model 1	1.04 (1.02 to 1.05)	<0.001
Model 2	1.04 (1.02 to 1.05)	<0.001
Model 3	1.03 (1.02 to 1.05)	<0.001
Model 4	1.03 (1.01 to 1.05)	0.002
$TBR^{<3.9\ mmol/L}$ (1% increase)		
Model 1	1.01 (0.98 to 1.04)	0.436
Model 2	1.01 (0.98 to 1.04)	0.523
Model 3	0.99 (0.96 to 1.03)	0.697
Model 4	1.01 (0.97 to 1.03)	0.751
$TBR^{<3.0\ mmol/L}$ (1% increase)		
Model 1	1.01 (0.92 to 1.10)	0.914
Model 2	1.00 (0.91 to 1.09)	0.927
Model 3	0.97 (0.87 to 1.07)	0.502
Model 4	0.98 (0.89 to 1.08)	0.663
LBGI (1-unit increase)		
Model 1	0.98 (0.90 to 1.07)	0.675
Model 2	0.98 (0.90 to 1.07)	0.623
Model 3	0.94 (0.85 to 1.03)	0.190
Model 4	0.98 (0.89 to 1.08)	0.683
HBGI (1-unit increase)		
Model 1	1.09 (1.06 to 1.13)	<0.001
Model 2	1.08 (1.05 to 1.11)	<0.001
Model 3	1.08 (1.05 to 1.12)	<0.001
Model 4	1.09 (1.04 to 1.13)	<0.001
MODD (1 mmol/L increase)		
Model 1	1.98 (1.62 to 2.43)	<0.001
Model 2	1.97 (1.59 to 2.44)	<0.001
Model 3	1.83 (1.42 to 2.37)	<0.001
Model 4	1.70 (1.26 to 2.29)	<0.001
IQR (1 mmol/L increase)		
Model 1	1.68 (1.44 to 1.98)	<0.001
Model 2	1.70 (1.44 to 2.01)	<0.001
Model 3	1.61 (1.42 to 1.97)	<0.001
Model 4	1.53 (1.21 to 1.93)	<0.001
HbA1c (1% increase)		
Model 1	1.68 (1.43 to 1.98)	<0.001
Model 2	1.56 (1.31 to 1.85)	<0.001
Model 3	1.39 (1.14 to 1.69)	0.001

Model 1: crude.
Model 2: adjusted for age, gender, BMI, and duration of diabetes.
Model 3: adjusted for variables in model 2 plus systolic blood pressure, total cholesterol, HDL cholesterol, logarithm of triglycerides, serum uric acid, estimated glomerular filtration rate, smoker, alcohol consumption, presence of diabetic retinopathy, use of insulin therapy, use of ACE inhibitors and/or angiotensin II receptor blockers, use of statins, and use of antiplatelet agents.
Model 4: adjusted for variables in model 3 plus HbA1c.
BMI, body mass index; CV, coefficient of variation; FLP-CGM, FreeStyle Libre Pro continuous glucose monitoring; HbA1c, hemoglobin A1c; HBGI, high blood glucose index; HDL, high-density lipoprotein; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; TAR, time above range; TBR, time below range; TIR, time in range.

even after adjusting for various possible risk factors including HbA1c, in patients with type 2 diabetes. The reason that those studies yielded conflicting results is not clear, but it may be due to differences in the characteristics of subjects or use of antidiabetic agents among studies. Previous studies enrolled patients with inadequately controlled type 2 diabetes; thus, the prevalence of albuminuria was relatively high, approximately 40%. In contrast, our subjects had a substantially lower prevalence of albuminuria (27%) and were more likely to be

taking SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists. Taken together, our data suggest that intraday and interday glucose variabilities are important targets in terms of reducing the risk of albuminuria in patients treated according to the current consensus about diabetes treatment.[34]

HbA1c is recognized as a gold standard for treatment target. A few studies have demonstrated strong associations between HbA1c levels and diabetic microvascular complications.[4 5] However, HbA1c alone may not adequately reflect an individual's glycemic variation and risk of hyperglycemia and hypoglycemia. In this regard, the ATTD Congress recommended TIR as a key metric of glycemic management in clinical practice.[15] Our results showed that $TIR^{3.9–10\ mmol/L}$, $TAR^{>10\ mmol/L}$, and $TAR^{>13.9\ mmol/L}$ are significantly associated with the severity of albuminuria, even after adjusting for possible risk factors including HbA1c levels. On the other hand, a recent study demonstrated that severe hypoglycemia is a predictor of worsening renal dysfunction in patients with type 2 diabetes.[35] However, in addition to LBGI, $TBR^{<3.9\ mmol/L}$ and $TBR^{<3.0\ mmol/L}$ were not associated with the severity of albuminuria in our study. Mild hypoglycemia, low frequency of hypoglycemic events, or both may not be involved in the development of albuminuria. Alternatively, the relatively low frequency of hypoglycemic events and short duration of hypoglycemia observed in our study may account for this finding. Taken together, based on FLP-CGM-derived metrics, focusing on improving hyperglycemia may be important to reduce the risk of albuminuria development. However, HbA1c alone does not provide enough information. Indeed, a previous study demonstrated that lower renal function (eGFR <60 mL/min/1.73 m^2) is strongly correlated with a higher prevalence of anemia in the general population.[36] Modest reductions in hemoglobin due to a shorter erythrocyte lifespan may affect the accuracy of HbA1c. In patients with more advanced DN, evaluating FLP-CGM-derived metrics could serve as a therapeutic target complementary to HbA1c.

Our study found that FLP-CGM-derived metrics related to glucose variability are associated with the severity of albuminuria, which is different from DR, even after adjusting for HbA1c levels. Although the exact reason for these findings is not clear, we postulated one scenario. Atherosclerosis of the intrarenal and extrarenal arteries and microangiopathy of the glomerular capillaries, afferent arterioles, and efferent arterioles are considered to contribute to the progression of glomerular lesions in DN.[37 38] Previous studies have demonstrated that glucose fluctuation is more significantly associated with atherosclerotic-related diseases than the degree of hyperglycemic exposure as indicated by HbA1c levels in patients with type 2 diabetes.[39 40] Thus, it is possible that atherosclerosis of the intrarenal and extrarenal arteries caused by glucose variability may also accelerate renal damage. Therefore, glucose variability is more likely to be associated with the pathogenesis of DN than DR.

The strengths of this study included its relatively large sample size and multicenter study design. Our study had certain limitations. First, the cross-sectional study design made it impossible to evaluate whether FLP-CGM-derived metrics had a causal relationship with diabetic microvascular complications. In this regard, we are currently conducting a long-term follow-up study in the same cohort that focuses on FLP-CGM-derived metrics and onset of outcomes such as primary cardiovascular disease and diabetic microvascular complications. Second, FLP-CGM-derived metrics were evaluated based on FLP-CGM measurements during a limited time. Thus, FLP-CGM-derived metrics may not represent overall glycemic control of subjects. In order to attain the best measurements of glucose fluctuations with FLP-CGM at baseline, we only recruited patients with stable control. In addition, we employed a blind CGM system that prevented subjects from altering their lifestyle behaviors based on the results of glucose readings. Third, we did not assess the accuracy of interstitial glucose levels obtained with the FLP-CGM system by comparing them with capillary glucose levels or venous glucose levels. Previous studies demonstrated some discrepancies in glucose levels obtained with the FLP-CGM system and conventional glucose measurements.[41–44] Thus, our findings should be interpreted with caution. Fourth, we only recruited Japanese patients with type 2 diabetes. These constraints may limit the generalizability of our results. Finally, some potential conventional risk factors for DR were not included in the multivariate regression analysis. Previous studies reported that inflammation and homocysteine contribute to DR progression.[45 46] This point should also be addressed in a future study.

CONCLUSION

In conclusion, we demonstrated that FLP-CGM-derived metrics related to intraday and interday glucose variability are significantly associated with the severity of DR and albuminuria, even after adjusting for various risk factors in patients with type 2 diabetes. Thus, these derived metrics could provide medical professionals with useful information for assessing the risk of severe diabetic microvascular complications. CGM might identify treatment targets in addition to those based on HbA1c.

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