Association Between Time in Range and HbA1c in Japanese Patients With Type 2 Diabetes Mellitus

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Abstract

There are no large-scale studies on the association between time in range (TIR) and hemoglobin A1c (HbA1c) in Japanese patients with type 2 diabetes mellitus (T2DM) only. The aim of this study was to define the relationship between TIR and HbA1c levels in Japanese patients with T2DM. The glycemic profile of 999 patients was analyzed with FreeStyle Libre Pro Continuous Glucose Monitoring (FLP-CGM) while they continued their prescribed glucose-lowering medications. FLP-CGM data recorded over 8 consecutive days were analyzed. The regression model for HbA1c on TIR was $\text{HbA1c} = 9.4966 - 0.0309 \times \text{TIR}$. The predicted HbA1c level for TIR of 70% was 7.33%, and is higher than recent reports subjecting mostly T1DM. The TIR corresponding to HbA1c 7.0% was 80.64%. HbA1c level correlated significantly with many FLP-CGM-derived metrics. The patients with low TIR tended to have long history of diabetes, on higher daily insulin dose and had high body mass index, HbA1c, liver dysfunction and triglyceride. Furthermore, relatively higher percentages of patients of this group used sulfonylureas, glinides, glucagon like peptide-1 receptor agonists and insulin. Our data showed that the predicted HbA1c corresponding to TIR is largely depends on the study population, thus is not uniform. Our results provide new insights on the management of T2DM.

Introduction

The UK Prospective Diabetes Study (UKPDS) 35 on patients with type 2 diabetes mellitus (T2DM) reported a linear relationship, without threshold values, between hemoglobin A1c (HbA1c) level and various T2DM-related complications, such as cardiovascular events¹. Furthermore, the Kumamoto study reported that patients with $\text{HbA1c} < 6.9\%$ were less likely to develop microangiopathy². These and other studies suggest that HbA1c can be used as an indicator of glycemic control in patients with T2DM. On the other hand, many large-scale clinical studies involving T2DM patients reported that reductions in HbA1c levels were more pronounced following intensive therapy compared with conventional therapy. While intensive therapy is reported to reduce the incidence of microangiopathy, it does not affect that of cardiovascular disease (CVD) events^{3,4}. In fact, one study reported a significant increase in the overall death rate with intensive therapy⁵. In addition, Currie et al.⁶ analyzed patients who were switched from monotherapy to combination oral glucose-lowering therapy or in whom insulin therapy was started. They reported that there was a U-shaped rather than a linear relationship between cardiovascular events and HbA1c levels, suggesting that there is a problem in relying on HbA1c only as an indicator of glycemic control in the treatment of diabetes.

In 2019, the international panel of the Advanced Technologies and Treatments for Diabetes (ATTD) Congress provided recommendations on glycemic control guidelines by Continuous Glucose Monitoring (CGM)⁷. According to the international guideline, the target range of blood glucose level is 70–180 mg/dL (except in pregnant women). Time in range (TIR) is defined as the time spent within the target range, and the time above range (TAR) and time below range (TBR) are defined as the time spent above and below the target range, respectively. Lu et al.⁸ investigated the association between TIR and intima-media

thickness ≥ 1.0 mm using the CGM data of 2215 patients. They reported significantly higher frequency of intima-media thickness ≥ 1.0 mm among patients with lower TIR. Furthermore, Beck et al.⁹ reanalyzed the 7-point self-monitored blood glucose data from the Diabetes Control and Complications Trial (DCCT) in order to determine the association between TIR and microangiopathy. They found higher frequencies of retinopathy and microalbuminuria among patients with low TIR.

While the association between TIR and diabetes-related complications has been assessed, as described above, to our knowledge, there are no large-scale studies on the association between TIR and HbA1c levels in patients with T2DM only. The aim of the present large multi-institutional study was to determine the relationship between TIR and HbA1c levels in T2DM.

Methods

Patients. The study population was Japanese patients with T2DM who regularly attended the Outpatient Diabetes Clinics of 34 institutions across Japan (listed in Supplementary Table 1). The study design, inclusion criteria and exclusion criteria had been published previously¹⁰. Patients who met the eligibility criteria were asked to participate in the present study. A total of 1,000 outpatients with T2DM, stable control and no history of apparent CVD were recruited between May 2018 and March 2019. One patient withdrew consent after enrollment. The study protocol was approved by the institutional review board of each participating institution in compliance with the Declaration of Helsinki and current legal regulations in Japan. Written informed consent was obtained from all participants after a full explanation of the study.

Study design. This study is an exploratory sub-analysis of an ongoing, observational, prospective cohort study designed to investigate the relationships between glucose variability evaluated with CGM and the incidence of composite cardiovascular events over a 5-year follow-up period, as described in detail previously¹⁰. The present study used baseline data from the cohort study and is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), which is a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors (UMIN000032325). All participants wore the FreeStyle Libre Pro (FLP) CGM (FLP-CGM) (FreeStyle Librepro®, Abbott Japan, Tokyo, Japan) for 14 days and the data used for analysis were obtained from days 4 to 11 of the FLP-CGM. No changes were made to diet or exercise therapy or glucose-lowering agents/insulin dose. The primary outcome was HbA1c predicted by TIR. The secondary outcomes were the correlation between HbA1c and FLP-CGM-derived metrics other than TIR, and the comparison of patient background for each TIR group.

Clinical laboratory tests. Fasting blood samples were obtained at outpatient visits and analyzed for renal function status, lipid levels, and HbA1c (National Glycohemoglobin Standardization Program) using standard techniques. Urinary albumin excretion (UAE) was measured using a latex agglutination assay on a spot urine sample. The estimated glomerular filtration rate (eGFR) was calculated using a standard formula¹¹.

CGM using FreeStyle Libre Pro Device. The FLP-CGM device was used in this study as reported previously¹⁰. Apart from wearing the FLP-CGM, no restrictions were imposed on the participants with respect to daily activities/routines. After the end of the 14-day recording, the CGM stored data were downloaded and analyzed. Glucose variability was assessed using the mean amplitude of glucose excursion (MAGE), SD, and coefficient of variation (CV). MAGE was calculated as the arithmetic mean of the differences between consecutive peaks and nadirs, provided that the differences were greater than one 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 protocol⁹. After the publication of the SAP, the ATTD Congress proposed some CGM-derived metrics as useful clinical targets that complement HbA1c⁷. Thus, we updated the SAP by adding certain CGM-derived metrics in this study prior to database lock. Mean glucose was measured from the data collected during FLP-CGM. TIR was defined as percentage of time spent within the target range of 70–180 mg/dl (time in range: TIR 70-180mg/dl), time above the target glucose range (TAR > 180 mg/dl, TAR > 250 mg/dl), and time below the target glucose range (TBR < 70 mg/dl, TBR < 54 mg/dl). Low blood glucose index (LBGI) and high blood glucose index (HBGI) formulae were implemented by converting glucose values into risk scores¹². In addition, the mean of daily differences (MODD)¹³ in glucose levels and interquartile range (IQR) were calculated to assess inter-day glucose variability. MODD was calculated as the mean of the absolute difference between glucose levels measured at the same time on two 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 four days of its 14-day lifetime¹⁴, we analyzed FLP-CGM data over the middle 8-day period, as stated above.

Statistical analysis. All variables are summarized as mean, standard deviation (SD), minimum and maximum for continuous variables and number (proportion) of patients for categorical variables. The Pearson correlation coefficient and linear regression model were used to assess the relationship between two variables. Continuous data were compared using analysis of variance and Kruskal-Wallis test, and categorical data were compared using χ^2 test and Fisher exact test. All statistical tests were two-sided with 5% significance level. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of study population. As reported in our previous study¹⁵, of the 999 participants, 608 were males. The mean age of participants was 64.6 ± 9.6 years, with duration of diabetes of 12.9 ± 8.5 years and HbA1c of $7.1 \pm 0.8\%$ (53.7 ± 8.8 mmol/mol). The participants were mildly obese, with mean BMI of 24.6 ± 3.9 kg/m². The average of glucose was 140.5 ± 32.3 mg/dl, SD of glucose was 36.7 ± 11.3 mg/dl, MAGE was 98.3 ± 36.1 mg/dl, TIR was $78.9 \pm 18.6\%$, TAR>180 was $19.0 \pm 19.2\%$, TBR<70 was $2.2 \pm 4.7\%$, HBGI was 5.6 ± 4.6 , LBGI was 1.6 ± 1.7 , MODD was 31.3 ± 11.5 mg/dl, and IQR was 38.6 ± 14.7 mg/dl. In addition, 89.5% had used glucose-lowering agents, including dipeptidyl peptidase 4 (DPP4) inhibitors (57.8%),

metformin (54.4%), sodium-glucose cotransporter 2 (SGLT2) inhibitors (23.1%), and sulfonylureas (12.7%), while 15.8% used insulin.

Relationship between TIR and HbA1c. We regressed HbA1c on TIR and the model was, $HbA1c = 9.4966 - 0.0309 \times TIR$. The predicted HbA1c level for a TIR of 70% was 7.33% (Table 1). The TIR corresponding to HbA1c 7.0% was 80.64%.

Table 1. Predicted HbA1c for a given TIR level

Intercept (a)	slope (b)	TIR (70-180 mg/dl)	Predicted HbA1c (%)
9.49	-0.03	20%	8.87
		30%	8.57
		40%	8.26
		50%	7.95
		60%	7.64
		70%	7.33
		80%	7.02
		90%	6.71

HbA1c: hemoglobin A1c, TIR: time in range.

Correlation between HbA1c and FLP-CGM-derived metrics and comparison of patient background for each TIR group. HbA1c level correlated significantly with many FLP-CGM-derived metrics, with the exception of CV and TBR<54 (Table 2, Fig. 1). Patients with low TIR tended to have a longer history of diabetes, be on higher daily insulin dose, and have higher BMI, HbA1c, alanine aminotransferase, gamma-glutamyl transpeptidase and triglyceride, as shown in Table 3. In addition, the complication rates of all microangiopathies were relatively higher in these patients, with more severe diabetic retinopathy and nephropathy. Furthermore, the incidence of use of sulfonylureas, glinides, glucagon like peptide-1 (GLP-1) receptor agonists, and insulin was likely to be higher in these patients (Table 4).

Table 2. Results of correlation analysis for HbA1c and parameters of glycemic fluctuation

variable 1	variable 2	r	95% CI for r
HbA1c	Average of glucose	0.74	(0.71, 0.77)
HbA1c	SD of glucose	0.53	(0.48, 0.57)
HbA1c	CV of glucose	0.03	(-0.04, 0.09)
HbA1c	MAGE	0.43	(0.38, 0.48)
HbA1c	Median of glucose	0.74	(0.71, 0.77)
HbA1c	Time in range 70-180 mg/dl	-0.71	(-0.74, -0.68)
HbA1c	Time below range below 70 mg/dl	-0.18	(-0.24, -0.12)
HbA1c	Time below range below 54 mg/dl	-0.05	(-0.11, 0.01)
HbA1c	Time above range above 180 mg/dl	0.73	(0.70, 0.76)
HbA1c	Time above range above 250 mg/dl	0.64	(0.60, 0.67)
HbA1c	HBGI	0.71	(0.68, 0.74)
HbA1c	LBGI	-0.25	(-0.31, -0.19)
HbA1c	MODD	0.59	(0.55, 0.63)
HbA1c	IQR	0.60	(0.55, 0.63)
HbA1c	Fasting plasma glucose	0.50	(0.45, 0.54)

r: Pearson correlation coefficient

HbA1c: hemoglobin A1c, CGM: continuous glucose monitoring, SD: standard deviation, CV: coefficient of variation, MAGE: mean amplitude of glucose excursion, LBGI: low blood glucose index, HBGI: high blood glucose index, MODD: mean of daily difference, IQR: interquartile range.

Table 3. Comparison of patient background according to TIR

parameter	TIR group	n	Mean	SD	Minimum	Maximum	P value (analysis of variance)	P value (Kruskal-Wallis)
Age (years)	<40%	54	60.3	10.2	39	78	0.001	<0.001
	40-49%	29	66.1	10.9	38	80		
	50-59%	57	64.9	10.4	35	80		
	60-69%	101	65.2	10.0	33	80		
	70-79%	147	66.7	9.2	34	80		
	≥80%	611	64.2	9.4	33	81		
	Total	999	64.6	9.6	33	81		
Diabetes duration (years)	<40%	54	12.8	7.7	2	37	<0.001	<0.001
	40-49%	29	15.5	7.7	2	36		
	50-59%	57	15.9	9.8	2	43		
	60-69%	101	13.6	7.5	2	35		
	70-79%	147	15.2	9.3	1	58		
	≥80%	611	11.8	8.2	1	46		
	Total	999	12.9	8.5	1	58		
Daily dose of insulin (unit/day)	<40%	19	22.5	13.2	6	61	0.006	0.008
	40-49%	10	24.2	27.8	8	101		
	50-59%	21	20.4	12.0	4	48		
	60-69%	21	14.5	10.8	4	48		
	70-79%	36	24.3	17.5	3	78		
	≥80%	51	13.9	8.0	3	36		

	Total	158	18.9	14.4	3	101		
BMI (kg/m ²)	<40%	54	25.96	4.53	17.8	36.9	0.019	0.043
	40-49%	29	25.36	3.89	18.5	34.1		
	50-59%	57	24.49	3.70	17.7	34.9		
	60-69%	101	23.79	3.43	17.1	36.0		
	70-79%	147	24.92	3.91	16.9	34.8		
	≥80%	611	24.52	3.85	16.3	40.8		
	Total	999	24.60	3.87	16.3	40.8		
HbA1c (%)	<40%	54	8.81	1.21	6.1	12.0	<0.001	<0.001
	40-49%	29	7.88	0.60	7.0	9.3		
	50-59%	57	7.73	0.72	5.2	9.7		
	60-69%	101	7.40	0.59	5.8	9.7		
	70-79%	147	7.16	0.55	5.7	9.0		
	≥80%	611	6.73	0.52	5.1	9.0		
	Total	999	7.06	0.81	5.1	12.0		
ALT (IU/l)	<40%	54	28.3	16.0	10	80	0.010	0.018
	40-49%	29	25.7	13.0	10	68		
	50-59%	57	26.4	16.4	4	97		
	60-69%	101	22.3	12.1	8	72		
	70-79%	147	24.2	13.4	9	72		
	≥80%	611	22.6	12.6	3	121		
	Total	999	23.4	13.2	3	121		

γ-GTP (IU/l)	<40%	54	46.2	51.0	9	254	0.011	0.033
	40-49%	29	46.0	62.3	9	349		
	50-59%	56	35.1	36.7	9	177		
	60-69%	101	34.4	35.3	9	277		
	70-79%	147	31.8	32.0	9	319		
	≥80%	609	30.9	30.8	6	393		
	Total	996	32.9	34.6	6	393		
TG (mg/dl)	<40%	54	187.8	171.8	48	868	<0.001	0.003
	40-49%	29	131.5	87.2	51	472		
	50-59%	57	136.8	119.5	35	749		
	60-69%	101	106.6	45.4	42	265		
	70-79%	147	127.7	71.4	39	432		
	≥80%	611	112.7	68.6	25	726		
	Total	999	120.3	82.1	25	868		

Abbreviations: HbA1c: hemoglobin A1c, ALT: alanine aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, TG: triglyceride, CGM: continuous glucose monitoring

Table 4. Proportions of microangiopathy and use of various glucose-lowering agents according to TIR

Diabetic neuropathy	TIR group	No	Yes	Total	P value*	P value [†]		
	<40%	27 (50.0)	27 (50.0)	54	<0.001	<0.001		
	40-49%	14 (48.3)	15 (51.7)	29				
	50-59%	31 (54.4)	26 (45.6)	57				
	60-69%	70 (69.3)	31 (30.7)	101				
	70-79%	101 (68.7)	46 (31.3)	147				
	≥80%	470 (76.9)	141 (23.1)	611				
	Total	713 (71.4)	286 (28.6)	999				
Diabetic retinopathy	TIR group	No	Yes	Total	P value*	P value [†]		
	<40%	32 (59.3)	22 (40.7)	54	<0.001	<0.001		
	40-49%	19 (65.5)	10 (34.5)	29				
	50-59%	39 (68.4)	18 (31.6)	57				
	60-69%	80 (79.2)	21 (20.8)	101				
	70-79%	108 (73.5)	39 (26.5)	147				
	≥80%	499 (81.7)	112 (18.3)	611				
	Total	777 (77.8)	222 (22.2)	999				
Diabetic retinopathy (right)	TIR group	NDR	SDR	PPDR	PDR	Total	P value*	P value [†]
	<40%	33 (61.1)	9 (16.7)	9 (16.7)	3 (5.6)	54	<0.001	<0.001
	40-49%	19 (65.5)	6 (20.7)	1 (3.4)	3 (10.3)	29		

	50-59%	40 (70.2)	7 (12.3)	5 (8.8)	5 (8.8)	57		
	60-69%	80 (79.2)	14 (13.9)	5 (5.0)	2 (2.0)	101		
	70-79%	108 (73.5)	24 (16.3)	6 (4.1)	9 (6.1)	147		
	≥80%	507 (83.0)	66 (10.8)	23 (3.8)	15 (2.5)	611		
	Total	787 (78.8)	126 (12.6)	49 (4.9)	37 (3.7)	999		
Diabetic retinopathy (left)	TIR group	NDR	SDR	PPDR	PDR	Total	P value*	P value [¶]
	<40%	32 (59.3)	9 (16.7)	9 (16.7)	4 (7.4)	5	<0.001	<0.001
	40-49%	19 (65.5)	7 (24.1)	1 (3.4)	2 (6.9)	29		
	50-59%	43 (75.4)	5 (8.8)	4 (7.0)	5 (8.8)	57		
	60-69%	83 (82.2)	11 (10.9)	4 (4.0)	3 (3.0)	101		
	70-79%	110 (74.8)	22 (15.0)	7 (4.8)	8 (5.4)	147		
	≥80%	505 (82.7)	69 (11.3)	23 (3.8)	14 (2.3)	611		
	Total	792 (79.3)	123 (12.3)	48 (4.8)	36 (3.6)	999		
Diabetic nephropathy	TIR group	No	Yes	Total	P value*	P value [¶]		
	<40%	32 (59.3)	22 (40.7)	54	<0.001	<0.001		
	40-49%	13 (44.8)	16 (55.2)	29				
	50-59%	31 (54.4)	26 (45.6)	57				
	60-69%	65 (64.4)	36 (35.6)	101				
	70-79%	104 (70.7)	43 (29.3)	147				
	≥80%	484	127	611				

		(79.2)	(20.8)				
	Total	729 (73.0)	270 (27.0)	999			
Diabetic nephropathy (stage)	TIR group	1	2	3	Total	P value*	P value [†]
	<40%	32 (59.3)	11 (20.4)	11 (20.4)	54	<0.001	<0.001
	40- 49%	13 (44.8)	13 (44.8)	3 (10.3)	29		
	50- 59%	31 (54.4)	16 (28.1)	10 (17.5)	57		
	60- 69%	65 (64.4)	31 (30.7)	5 (5.0)	101		
	70- 79%	104 (70.7)	33 (22.4)	10 (6.8)	147		
	≥80%	484 (79.2)	99 (16.2)	28 (4.6)	611		
	Total	729 (73.0)	203 (20.3)	67 (6.7)	999		
SGLT2 inhibitor	TIR group	No	Yes	Total	P value*	P value [†]	
	<40%	39 (72.2)	15 (27.8)	54	0.012	0.019	
	40- 49%	15 (51.7)	14 (48.3)	29			
	50- 59%	46 (80.7)	11 (19.3)	57			
	60- 69%	73 (72.3)	28 (27.7)	101			
	70- 79%	111 (75.5)	36 (24.5)	147			
	≥80%	484 (79.2)	127 (20.8)	611			
	Total	768 (76.9)	231 (23.1)	999			
Sulfonylurea	TIR group	No	Yes	Total	P value*	P value [†]	
	<40%	45	9	54	<0.001	<0.001	

		(83.3)	(16.7)			
	40-49%	21 (72.4)	8 (27.6)	29		
	50-59%	49 (86.0)	8 (14.0)	57		
	60-69%	77 (76.2)	24 (23.8)	101		
	70-79%	122 (83.0)	25 (17.0)	147		
	≥80%	558 (91.3)	53 (8.7)	611		
	Total	872 (87.3)	127 (12.7)	999		
Glinide	TIR group	No	Yes	Total	P value*	P value [†]
	<40%	46 (85.2)	8 (14.8)	54	0.025	0.020
	40-49%	27 (93.1)	2 (6.9)	29		
	50-59%	51 (89.5)	6 (10.5)	57		
	60-69%	94 (93.1)	7 (6.9)	101		
	70-79%	132 (89.8)	15 (10.2)	147		
	≥80%	581 (95.1)	30 (4.9)	611		
	Total	931 (93.2)	68 (6.8)	999		
GLP-1 receptor agonist	TIR group	No	Yes	Total	P value*	P value [†]
	<40%	48 (88.9)	6 (11.1)	54	0.004	0.001
	40-49%	25 (86.2)	4 (13.8)	29		
	50-59%	49 (86.0)	8 (14.0)	57		
	60-69%	89 (88.1)	12 (11.9)	101		

	70-79%	132 (89.8)	15 (10.2)	147		
	≥80%	582 (95.3)	29 (4.7)	611		
	Total	925 (92.6)	74 (7.4)	999		
Insulin	TIR group	No	Yes	Total	P value*	P value [¶]
	<40%	35 (64.8)	19 (35.2)	54	<0.001	<0.001
	40-49%	19 (65.5)	10 (34.5)	29		
	50-59%	36 (63.2)	21 (36.8)	57		
	60-69%	80 (79.2)	21 (20.8)	101		
	70-79%	111 (75.5)	36 (24.5)	147		
	≥80%	560 (91.7)	51 (8.3)	611		
	Total	841 (84.2)	158 (15.8)	999		

Data are number (percentage) of patients.

*by χ^2 test, [¶]by Fisher's exact test

SGLT2 inhibitor: sodium-glucose cotransporter 2 inhibitor, GLP-1: glucagon like peptide-1, NDR: non-diabetic retinopathy, SDR: simple diabetic retinopathy, PDR: proliferative diabetic retinopathy, PPDR: pre-proliferative diabetic retinopathy

Discussion

In the present study, we investigated the association between TIR and HbA1c using FLP-CGM in Japanese patients with T2DM in real-world clinical practice and their association with patient characteristics.

There are two important American studies on the association between TIR and HbA1c levels. Beck et al.¹⁶ studied 545 patients with T1DM while Vigersky and McMahon¹⁷ conducted a meta-analysis of 18 CGM-based studies, including a total of 1137 patients (927 and 210 patients with T1DM and T2DM, respectively). Beck et al.¹⁶ predicted HbA1c that corresponded to TIR of 70% to be 7.0% (HbA1c

decreased by 0.5% for each 10% increase in TIR). On the other hand, Vigersky and McMahon¹⁷ reported that the predicted HbA1c corresponding to TIR of 70% was 6.7% (HbA1c decreased by 0.8% for each 10% increase in TIR). In the present study, the predicted HbA1c corresponding to TIR of 70% was 7.33%, and HbA1c decreased by 0.3% for each 10% increase in TIR. Thus, the predicted HbA1c corresponding to TIR of 70% in the present study was higher than that reported in the above two previous studies. In the present study, the predicted HbA1c corresponding to TIR of 70% and the mean TIR were higher and mean values of TAR and TBR were lower than those reported in the above studies. There are several possible explanations for these results. First, this could be due to limiting the present study to only patients with T2DM, and the low proportion of patients using insulin (which was only 15.8%). Second, in the previous report^{16,17}, CGMs such as Dexcom were used, but in this study, we used FLP-CGM, which does not require calibration. So the difference in the sensor used may have been related. Howard R et al. reported that FLP-CGM tended to produce lower mean blood glucose levels than Dexcom G4 Platinum¹⁸, and Nagl K et al. reported that FLP-CGM had a greater mean absolute relative difference (MARD) and lower mean glucose levels than Dexcom G6 and Medtronic Enlite¹⁹. Third, the subjects of this study were Japanese patients with T2DM, and racial differences may also be relevant. Herman WH demonstrated studies that have compared HbA1c levels by race have consistently demonstrated higher HbA1c levels in African Americans than in whites²⁰. Bergenstal RM et al. reported that the average blood glucose level measured by CGM was lower in black participants than in white participants for the same HbA1c level. The possibility that the equation for the relationship between mean blood glucose and HbA1c differs by race and ethnicity was discussed²¹. To date, there are no large-scale data using FLP-CGM in Japanese patients with T2DM, and further data accumulation is needed. Also, the HbA1c prediction formula by TIR, which is the primary outcome in the present study, was $HbA1c = 9.4966 - 0.0309 \times TIR$, and the TIR corresponding to HbA1c 7.0% was 80.64%. According to the international guideline⁷, the recommended TIR is $\geq 70\%$ not only for patients with T1DM but also for those with T2DM. Our findings suggest that the TIR should be $\geq 80\%$ in order to achieve an HbA1c level of $< 7.0\%$ in Japanese patients with T2DM on medications associated with low risk of hypoglycemia.

A recent study on 6225 patients with T2DM based on CGMS Gold reported that the total mortality rate was 1.23 times higher in those with TIR between 71% and 85%, 1.30 times higher in those with values between 51% and 80%, and 1.83 times higher in those with values $\leq 50\%$, compared to those with TIR $> 85\%$ ²². And they reported that cardiovascular mortality was 1.35 times higher in those with TIR between 71% and 85%, 1.47 times higher in those with values between 51% and 80%, and 1.85 times higher in those with values $\leq 50\%$, compared to those with TIR $> 85\%$. Furthermore, they compared patient characteristics according to TIR ($> 85\%$, 71%-85%, 51%-80%, and $\leq 50\%$)²². Patients with low TIR had a longer history of diabetes, higher HbA1c and TG levels, and a larger percentage used insulin, than the other TIR groups. These results confirmed the early findings of Lu et al.²³ However, the use of glucose-lowering medications was not analyzed in the previous studies. In the present study, higher percentages of patients with low TIR used sulfonylureas, GLP-1 receptor agonists, and insulin, compared to the other TIR groups. According to the basic data collected in 2019 by the Japan Diabetes Clinical Data

Management (JDDM) Study group, many T2DM patients treated with insulin or GLP-1 receptor agonists exhibited poor control of HbA1c ($\geq 8\%$), indicating that the present findings are consistent with the real-world data. In the treatment of diabetes in Japan, sulfonylureas, insulin, and GLP-1 receptor agonists are considered to reflect the fact that they are often administered to T2DM patients with poor glycemic control. Including these drugs, we believe that active therapeutic intervention from an early stage is important to achieve the target glycemic control.

The strength of this study is its relatively large-sample, multicenter, study design. However, our study has certain limitations. First, FLP-CGM derived metrics were evaluated by 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 of measurements of glucose fluctuation by FLP-CGM at baseline, we employed a blind CGM system that enable subjects not to alter their lifestyle behaviors based on the results of glucose readings. Second, this study used FLP-CGM, which does not require calibration, and the mean glucose level may have been lower due to the difference in the sensor used. Third, this study was conducted on Japanese patients with T2DM, and racial differences should be considered. In the present study, the predicted HbA1c corresponding to TIR of 70% and the mean TIR were higher and mean values of TAR and TBR were lower than those reported in previous studies. We only recruited Japanese patients with T2DM, and the low proportion of patients using insulin. These constraints may limit the generalizability of our results.

Conclusion

There are no large-scale studies that have evaluated the association between TIR and HbA1c levels in patients with T2DM only. To our knowledge, this multi-institutional study of 999 patients with T2DM only is the largest and the results provide new insights on the management of T2DM.

Declarations

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Author contributions

A.K, Y.O, T.M, S.W and H.W conceived and designed this study. T.M, S.W and M.G acquired, analyzed and interpreted the data. A.K drafted the main manuscript text and prepared tables and figures. Y.O, T.M, S.W, N.K, H.Y, K.K, K.N, S.M, Y.T, M.G and I.S revised the manuscript. H.W supervised the manuscript. All authors reviewed the manuscript.

Competing interest

H.W. has received research funds from Abbott Japan. H.W. is a member of the advisory board of Abbott Japan. All other authors declare no conflict of interest.

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Figures

Figure 1.

Figure 1

The correlation between HbA1c level and FLP-CGM-derived metrics. (A) TIR, (B) average blood glucose, (C) TAR>180, (D) TAR>250.

Supplementary Files

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