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Association of time in range with hemoglobin A1c, glycated albumin and 1,5-anhydro-D-glucitol

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ABSTRACT

Aims/Introduction: Hemoglobin A1c (HbA1c), glycated albumin (GA) and 1,5-anhydro-D-glucitol (1,5-AG) are used as indicators of glycemic control, whereas continuous glucose monitoring (CGM) is used to assess daily glucose profiles. The aim of this study was to investigate the relationships between CGM metrics, such as time in range (TIR), and glycemic control indicators.

Materials and Methods: We carried out retrospective CGM and blood tests on 189 outpatients with impaired glucose tolerance (n = 22), type 1 diabetes mellitus (n = 67) or type 2 diabetes mellitus (n = 100).

Results: In type 1 diabetes mellitus and type 2 diabetes mellitus patients, HbA1c and GA were negatively correlated with TIR, whereas 1,5-AG was positively correlated with TIR. In type 1 diabetes mellitus patients, a TIR of 70% corresponded to HbA1c, GA and 1,5-AG of 6.9% (95% confidence interval [CI] 6.5–7.2%), 20.3% (95% CI 19.0–21.7%) and 6.0 μg/mL (95% CI 5.1–6.9 μg/mL), respectively. In type 2 diabetes mellitus patients, a TIR of 70% corresponded to HbA1c, GA and 1,5-AG of 7.1% (95% CI 7.0–7.3%), 19.3% (95% CI 18.7–19.9%) and 10.0 μg/mL (95% CI 9.0–11.0 μg/mL), respectively. TIR values corresponding to HbA1c levels of 7.0% were 56.1% (95% CI 52.3–59.8%) and 74.2% (95% CI 71.3–77.2%) in type 1 diabetes mellitus and type 2 diabetes mellitus patients, respectively.

Conclusions: The results of this study showed that the estimated HbA1c corresponding to a TIR of 70% was approximately 7.0% for both type 1 diabetes mellitus and type 2 diabetes mellitus patients, and that the estimated 1,5-AG calculated from the TIR of 70% might be different between type 1 diabetes mellitus and type 2 diabetes mellitus patients.

INTRODUCTION

The purpose of diabetes treatment is to maintain good glycemic control from the early stage of diabetes, and to prevent the onset and progression of diabetic microvascular complications and arteriosclerotic diseases[1,2]. Hemoglobin A1c (HbA1c) is the most commonly used evaluation method of blood glucose control in clinical treatment, and HbA1c is currently recognized as the key surrogate marker for the development of long-term diabetic complications in patients with diabetes. In fact, it is possible to prevent the onset and progression of diabetic complications by achieving good glycemic control by using HbA1c as an indicator[3,4]. It has been reported that although HbA1c merely shows the mean blood glucose levels, it is insufficient for evaluation of hypoglycemia and acute glycemic excursions[5–10]. Furthermore, previous studies have reported that several conditions, such as iron deficiency, anemia and chronic kidney disease, might affect HbA1c concentrations, independent of blood glucose levels[11–13].

Glycated albumin (GA) and 1,5-anhydro-D-glucitol (1,5-AG) are also commonly used evaluation methods of glycemic control. GA is a ketoamine formed through a non-enzymatic glycation reaction of serum albumin, and it reflects short- to

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intermediate-term mean blood glucose levels due to the half-life time of the albumin, which is approximately 2–3 weeks[14,15]. GA is also known to more sensitively reflect postprandial hyperglycemia than HbA1c[15,16]. 1,5-AG is a metabolically inert polyol that competes with glucose for reabsorption in the kidneys[17]. Thus, low values of 1,5-AG reflect high blood glucose levels[17]. 1,5-AG can be used as a potential marker for short-term blood glucose levels due to its half-life of approximately 1–2 weeks[18]. Furthermore, several studies reported that 1,5-AG reflects the postprandial glucose levels in patients with diabetes, and is more sensitive and specific than HbA1c[19].

Recently, continuous glucose monitoring (CGM) is increasingly used in the management of patients with diabetes, with advances in CGM technology. CGM can provide detailed information about glucose variability[20]. The international consensus report on clinical targets for CGM data interpretation has been developed and widely recognized[21]. This consensus statement mentioned that time in range (TIR), time below range (TBR) and time above range (TAR) are appropriate and useful as clinical targets and outcome measurements that complement HbA1c for a wide range of patients with diabetes[21].

However, few studies have examined the relationship between TIR and HbA1c or between TIR and either GA or 1,5-AG. The purpose of the present study was to investigate the relationships between CGM metrics, such as TIR, and glycemic control indicators, such as HbA1c, GA and 1,5-AG.

METHODS

Participants

The present study included patients with type 1 diabetes mellitus, type 2 diabetes mellitus and impaired glucose tolerance (IGT) between the age of 20 and 80 years who regularly visited the outpatient department of Hyogo College of Medicine Hospital, Nishinomiya, Japan. Diagnosis of diabetes or IGT was made in accordance with the diabetes diagnostic criteria of the Japan Diabetes Society[22]. The exclusion criteria were as follows: (i) those with severe hepatic dysfunction (defined as alanine transaminase ≥3-fold the upper limit of normal); (ii) those with chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2) or nephrotic syndrome; (iii) those diagnosed with anemia; (iv) pregnant women; (v) those taking sodium–glucose cotransporter 2 inhibitors; and (vi) those deemed ineligible for this study by their physician. A total of 189 eligible patients were enrolled in the study between January 2017 and August 2019. The present study was carried out after approval from the ethics committee of Hyogo College of Medicine. The committee approved the use of the opt-out approach to consent in the hospital.

Retrospective CGM

CGM studies were carried out using FreeStyle Libre Pro® (Abbott Japan, Tokyo, Japan). Each patient was instructed to wear a CGM device for 14 days, and all sensor glucose data obtained were used. Then, mean sensor glucose, standard deviation (SD), coefficient of variation (CV), the continuous overlapping net glycemic action calculated every 1 h[22], ratio of sensor glucose levels between 70 mg/dL and 180 mg/dL (time in range; $TIR^{70–180}$), ratio of sensor glucose levels >180 mg/dL (time above range; $TAR^{>180}$), ratio of sensor glucose levels >250 mg/dL ($TAR^{>250}$), ratio of sensor glucose levels <70 mg/dL (time below range; $TBR^{<70}$), ratio of sensor glucose levels <54 mg/dL ($TBR^{<54}$) were calculated.

Measurement of HbA1c, GA, and 1,5-AG

Blood tests for HbA1c and other biological markers were conducted on the day of CGM application. HbA1c was measured with high-performance liquid chromatography using HLC-723G11 (Tosoh Corporation, Tokyo, Japan). GA was measured by the enzymatic method using Lucica® Glycated Albumin-L (Asahi Kasei Pharma Corporation, Tokyo, Japan) as a measuring reagent and Cobas 8000 modular analyzer (Roche Diagnostics K.K., Tokyo, Japan) as a measuring instrument. 1,5-AG was measured by the enzymatic method using Deteminer L 1,5-AG (Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan) as a measuring reagent and JCA-BM 8000 automatic analyzer (Japan Electron Optics Laboratories, Tokyo, Japan) as measuring equipment. The lower detection limit of 1,5-AG was 1.0 μg/mL, and values ≤1.0 μg/mL were defined as 1.0 μg/mL in this study.

Statistical analysis

The three groups (type 1 diabetes mellitus, type 2 diabetes mellitus, and IGT) were compared using the Kruskal–Wallis test, whereas type 2 diabetes mellitus and IGT were compared with type 1 diabetes mellitus using the Steel′s test. Spearman′s rank correlation coefficient was used to determine correlations between two variables. In type 1 diabetes mellitus, a multiple regression analysis was conducted using $TIR^{70–180}$ as the objective variable and age, gender, body mass index (BMI), HbA1c, and types of insulin therapy as explanatory variables. In type 2 diabetes mellitus, a multiple regression analysis was also conducted using $TIR^{70–180}$ as the objective variable and age, sex, BMI, HbA1c, and types of diabetes therapy as explanatory variables. Least squares regression models were used to assess the relationship between CGM metrics and HbA1c, GA, and 1,5-AG. Statistical analyses were conducted using the BellCurve software version 2.15 (Social Survey Research Information Co., Ltd., Tokyo, Japan), with $P < 0.05$ indicating statistical significance.

RESULTS

Participant background

Results are given as median (interquartile range) unless otherwise stated. The characteristics of the participants are shown in Table 1. There were 189 subjects, consisting of 89 females and 100 males. Table 1 shows the status of use of hypoglycemic agents. All patients with type 1 diabetes mellitus were on insulin, with 62.7% of them receiving multiple daily insulin

Table 1 | Participant characteristics

	Total	Type 1 diabetes mellitus	Type 2 diabetes mellitus	IGT	*P*
n (female : male)	189 (89:100)	67 (48:19)	100 (31:69)	22 (10:12)	
Age (years)	66 (51–71)	42 (32–56)	69 (65–72)*	71 (67–73)*	<0.01
BMI (kg/m^2)	23.0 (21.0–24.8)	21.6 (19.4–23.9)	23.7 (21.7–25.1)*	23.8 (22.4–25.4)*	<0.01
eGFR (mL/min/1.73 m^2)	78.0 (66.0–94.0)	98.0 (82.0–116.0)	71.0 (62.0–82.0)*	66.0 (59.3–72.8)*	<0.01
Types of therapy (%)					
Metformin	24.9	0	47.0	0	
SU/glinides	13.2	0	25.0	0	
TZD	3.7	0	7.0	0	
α-GI	7.4	0	14.0	0	
DPP-4i	25.9	0	49.0	0	
Insulin	68.8	100	30.0	0	
GLP-1 RA	5.3	0	10.0	0	

The results are presented as the median (interquartile range). Three groups were compared using the Kruskal–Wallis test. Type 2 diabetes mellitus and impaired glucose tolerance (IGT) were compared with type 1 diabetes mellitus using Steel's test. BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SU, sulfonylureas; TZD, thiazolidines; α-GI, alpha-glucosidase inhibitors. *$P < 0.05$, versus type 1 diabetes mellitus patients.

Table 2 | Results of glycemic control indicators and continuous glucose monitoring metrics

	Total	Type 1 diabetes mellitus	Type 2 diabetes mellitus	IGT	*P*
HbA1c (%)	6.9 (6.5–7.7)	7.6 (6.9–8.6)	6.9 (6.4–7.5)*	6.0 (5.7–6.1)*	<0.01
GA (%)	19.4 (16.7–22.8)	23.5 (21.5–26.2)	17.7 (15.5–19.7)*	14.6 (13.7–15.4)*	<0.01
1,5-AG (μg/mL)	7.2 (4.0–14.3)	4.0 (2.0–5.3)	8.7 (3.0–15.3)*	18.1 (14.6–20.9)*	<0.01
Mean SG (mg/dL)	146.1 (120.8–172.0)	169.6 (151.0–203.0)	140.4 (119.8–160.5)*	108.4 (99.1–112.8)*	<0.01
SD (mg/dL)	47.3 (35.6–69.8)	75.8 (61.9–85.6)	41.3 (34.6–49.7)*	25.9 (20.6–34.6)*	<0.01
CV (%)	32.1 (27.0–41.6)	43.8 (35.6–46.2)	29.4 (25.4–32.5)*	25.0 (20.6–29.9)*	<0.01
CONGA-1 (mg/dL)	35.4 (31.1–45.1)	45.3 (40.1–51.5)	33.8 (30.0–37.3)*	25.5 (22.3–32.6)*	<0.01
TIR$^{70–180}$ (%)	70.1 (49.7–87.5)	49.3 (38.0–59.3)	76.2 (66.2–87.9)*	92.9 (90.1–97.1)*	<0.01
TAR$^{>180}$ (%)	25.5 (7.5–42.0)	42.0 (31.9–57.5)	18.2 (6.5–29.89)*	1.7 (0.3–7.2)*	<0.01
TAR$^{>250}$ (%)	6.8 (2.3–16.1)	19.1 (10.3–31.8)	5.0 (1.8–10.5)*	0.9 (0.4–2.2)*	<0.01
TBR$^{<70}$(%)	2.3 (0.2–6.9)	4.8 (2.1–11.6)	0.8 (0–4.0)*	1.9 (0.5–6.7)	<0.01
TBR$^{<54}$(%)	0.1 (0–1.4)	1.3 (0.2–3.9)	0 (0–0.6)*	0 (0–0.6)*	<0.01

The results are presented as median (interquartile range). Three groups were compared using the Kruskal–Wallis test. Type 2 diabetes mellitus and impaired glucose tolerance (IGT) were compared with type 1 diabetes mellitus using Steel's test. 1,5-AG, 1,5-anhydro-D-glucitol; CONGA-1, the continuous overlapping net glycemic action calculated every 1 h; CV, coefficient of variation; GA, glycated albumin; SD, standard deviation; SG, sensor glucose; TAR$^{>180}$, time above range >180 mg/dL; TAR$^{>250}$, time above range >250 mg/dL; TBR$^{<54}$, time below range <54 mg/dL; TBR$^{<70}$, time below range <70 mg/dL; TIR$^{70–180}$, time in range 70–180 mg/dL. *$P < 0.05$, versus type 1 diabetes mellitus.

injections and 37.3% being on continuous subcutaneous insulin infusions. In patients with type 2 diabetes mellitus, higher proportions of DPP-4 inhibitors and metformin were used, with 30% of them using insulin.

Table 2 shows the HbA1c, GA, and 1,5-AG levels and CGM metrics. HbA1c levels were significantly higher in type 1 diabetes mellitus [7.6 (6.9, 8.6) %] than in type 2 diabetes mellitus [6.9 (6.4, 7.5) %] and IGT [6.0 (5.7, 6.1) %] ($P < 0.01$). GA levels were also highest in type 1 diabetes mellitus. In contrast, 1,5-AG levels were significantly lower in type 1 diabetes mellitus [4.0 (2.0, 5.3) μg/mL] than in type 2 diabetes mellitus [8.7 (3.0, 15.3) μg/mL] and IGT [18.1 (14.6, 20.9) μg/mL] ($P < 0.01$). TIR$^{70–180}$ was significantly lower in type 1 diabetes mellitus [49.3 (38.0, 59.3) %] than in type 2 diabetes mellitus [76.2 (66.2, 87.9) %] and IGT [92.9 (90.1, 97.1) %] ($P < 0.01$). The proportion of patients with TIR$^{70–180}$ >70% was 100% in IGT and 68.0% in type 2 diabetes mellitus, but only 10.4% in type 1 diabetes mellitus. In addition, among patients with HbA1c levels of ≤7.0%, only 27.3% of those with type 1 diabetes mellitus had TIR$^{70–180}$ of >70%, whereas 86.2% of those with type 2 diabetes mellitus had TIR$^{70–180}$ of >70%. TAR$^{>180}$ and TAR$^{>250}$ were similarly highest in type 1 diabetes mellitus. TBR$^{<70}$ was significantly higher in type 1 diabetes mellitus [4.8 (2.1, 11.6) %] than in type 2 diabetes mellitus [0.8 (0, 4.0) %] ($P < 0.01$), but not significantly different from that found in IGT [1.9 (0.5, 6.7) %] ($P = 0.15$). The proportion of patients

Table 3 | Correlations between continuous glucose monitoring metrics and glycemic control indicators

	HbA1c	GA	1,5-AG	SD	CV	CONGA 1	$TIR^{70–180}$	$TAR^{>180}$	$TBR^{<70}$
Type 1 diabetes mellitus									
HbA1c	–	0.85*	−0.64*	0.52*	−0.08	0.35*	−0.62*	0.66*	−0.44*
GA	0.85*	–	−0.61*	0.49*	−0.11	0.30*	−0.67*	0.66*	−0.41*
1,5-AG	−0.64*	−0.61*	–	−0.50*	−0.07	−0.46*	0.57*	−0.53*	0.30*
SD	0.52*	0.49*	−0.50*	–	0.45	0.76*	−0.77*	0.66*	−0.16
CV	−0.08	−0.11	−0.07	0.45*	–	0.22	0.05	−0.28*	0.74*
CONGA-1	0.35*	0.30*	−0.46*	0.76*	0.22	–	−0.67*	0.61*	−0.30*
$TIR^{70–180}$	−0.62*	−0.67*	0.57*	−0.77*	0.05	−0.67*	–	−0.93*	0.52*
$TAR^{>180}$	0.66*	0.66*	−0.53*	0.66*	−0.28	0.61*	−0.93*	–	−0.74*
$TBR^{<70}$	−0.44*	−0.41*	0.30*	−0.16	0.74	−0.30*	0.52*	−0.74*	–
Type 2 diabetes mellitus									
HbA1c	–	0.63*	−0.59*	0.53*	−0.15	0.37*	−0.56*	0.74*	−0.48*
GA	0.63*	–	−0.44*	0.63*	0.05	0.46*	−0.55*	0.70*	−0.31*
1,5-AG	−0.59*	−0.44*	–	−0.48*	−0.11	−0.28*	0.56*	−0.51*	0.14
SD	0.53*	0.63*	−0.48*	–	0.53*	0.73*	−0.74*	0.78*	0.01
CV	−0.15	0.05	−0.11	0.53*	–	0.38*	−0.12	−0.08	0.71*
CONGA-1	0.37*	0.46*	−0.28*	0.73*	0.38*	–	−0.46*	0.58*	−0.04
$TIR^{70–180}$	−0.56*	−0.55*	0.56*	−0.74*	−0.12	−0.46*	–	−0.83*	0.13
$TAR^{>180}$	0.74*	0.70*	−0.51*	0.78*	−0.08	0.58*	−0.83*	–	−0.50*
$TBR^{<70}$	−0.48*	−0.31*	0.14	0.01	0.71*	−0.04	0.13	−0.50*	–

Spearman's rank correlation coefficient was used to determine correlations between two variables. 1,5-AG, 1,5-anhydro-D-glucitol; CONGA-1, the continuous overlapping net glycemic action calculated every 1 h; CV, coefficient of variation; GA, glycated albumin; SD, standard deviation; $TAR^{>180}$, time above range >180 mg/dL; $TBR^{<70}$, time below range <70 mg/dL; $TIR^{70–180}$, time in range 70–180 mg/dL. *$P < 0.05$.

with $TBR^{<70}$ ≥4% was 26.0% in type 2 diabetes mellitus and 55.2% in type 1 diabetes mellitus. Although no antidiabetic drugs were used in all IGT patients, $TBR^{<70}$ ≥4% was observed in 40.9% of them.

Correlations between glycemic control indicators and time in range

Correlations between $TIR^{70–180}$, $TAR^{>180}$, $TBR^{<70}$, and glycemic control indicators such as HbA1c were investigated (Table 3).

Table 4 | Estimation of hemoglobin A1c from continuous glucose monitoring metrics

	Type 1 diabetes mellitus			Type 2 diabetes mellitus		
	HbA1c (%)	95% CI	95% PI	HbA1c (%)	95% CI	95% PI
$TIR^{70–180}$						
50%	7.7	(7.5–7.9)	(6.1–9.3)	7.7	(7.4–7.9)	(6.4–8.9)
70%	6.9	(6.5–7.2)	(5.2–8.5)	7.1	(7.0–7.3)	(5.9–8.4)
	$HbA1c = 9.75 - 0.04 \times TIR^{70–180}$			$HbA1c = 8.93 - 0.03 \times TIR^{70–180}$		
	$R = 0.64$, $R^2 = 0.41$, RMSE = 0.80			$R = 0.60$, $R^2 = 0.36$, RMSE = 0.64		
$TAR^{>180}$						
25%	7.1	(6.8–7.3)	(5.5–8.7)	7.1	(7.0–7.2)	(6.0–8.2)
50%	7.9	(7.7–8.1)	(6.4–9.5)	7.9	(7.7–8.1)	(6.8–9.0)
	$HbA1c = 6.21 + 0.03 \times TAR^{>180}$			$HbA1c = 6.38 + 0.03 \times TAR^{>180}$		
	$R = 0.66$, $R^2 = 0.43$, RMSE = 0.79			$R = 0.73$, $R^2 = 0.54$, RMSE = 0.54		
$TBR^{<70}$						
1%	8.1	(7.8–8.4)	(6.1–10.1)	7.2	(7.0–7.3)	(5.7–8.6)
4%	7.9	(7.7–8.2)	(6.0–9.9)	7.1	(6.9–7.2)	(5.6–8.6)
	$HbA1c = 8.15 - 0.06 \times TBR^{<70}$			$HbA1c = 7.21 - 0.04 \times TBR^{<70}$		
	$R = 0.37$, $R^2 = 0.14$, RMSE = 0.97			$R = 0.40$, $R^2 = 0.16$, RMSE = 0.73		

The least squares method was used to estimate hemoglobin A1c (HbA1c) from time in range (TIR), time above range (TAR) and time below range (TBR). 95% CI, 95% confidence interval; 95% PI, 95% prediction interval; R, multiple correlation coefficient; R^2, coefficient of determination; RMSE, root mean square error; $TAR^{>180}$, time above range >180 mg/dL; $TBR^{<70}$, time below range <70 mg/dL; $TIR^{70–180}$, time in range 70–180 mg/dL.

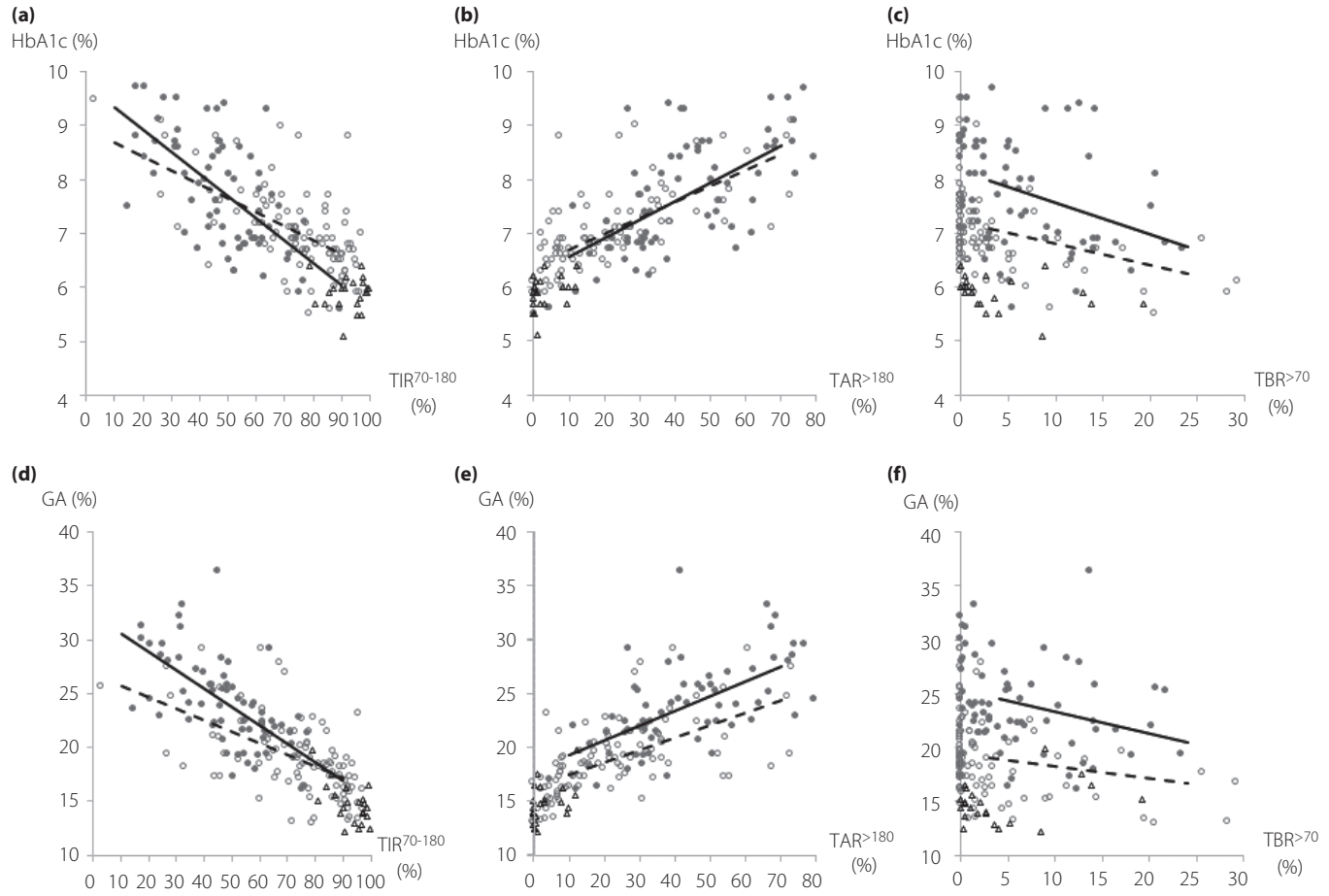

Figure 1 | Association of hemoglobin A1c (HbA1c) and glycated albumin (GA) with time in range (TIR), time above range (TAR), and time below range (TBR). ●, Type 1 diabetes mellitus; ○, type 2 diabetes mellitus; Δ, impaired glucose tolerance; solid line, single regression line in type 1 diabetes mellitus patients; broken line, single regression lines in type 2 diabetes mellitus patients. (a) Association between HbA1c and $TIR^{70–180}$. (b) Association between HbA1c and $TAR^{>180}$. (c) Association between HbA1c and $TBR^{<70}$. (d) Association between GA and $TIR^{70–180}$. (e) Association between GA and $TAR^{>180}$. (f) Association between GA and $TIR^{<70}$.

In type 1 diabetes mellitus and type 2 diabetes mellitus, $TIR^{70–180}$ was negatively correlated with HbA1c, GA, standard deviation, and continuous overlapping net glycemic action calculated every 1 h but positively correlated with 1,5-AG. In addition, in type 1 diabetes mellitus and type 2 diabetes mellitus, $TAR^{>180}$ was positively correlated with HbA1c, GA, SD, and continuous overlapping net glycemic action calculated every 1 h, but negatively correlated with 1,5-AG and $TBR^{<70}$ was negatively correlated with HbA1c and GA; however, there was no correlation between $TBR^{<70}$ and 1,5-AG in type 2 diabetes mellitus patients.

In type 1 diabetes mellitus, multiple regression analyses were carried out with $TIR^{70–180}$ as the objective variable, and HbA1c, types of diabetes therapy and so on as explanatory variables (Table S1). As a result, HbA1c (standardized partial regression coefficient; $\beta = -0.66$, $P < 0.01$) was more useful as an explanatory variable for $TIR^{70–180}$ than types of insulin therapy ($\beta = 0.06$, $P = 0.59$). A similar multiple regression analysis was carried out in type 2 diabetes mellitus patients, and HbA1c ($\beta = -0.56$, $P < 0.01$) was also found useful as an explanatory variable for $TIR^{70–180}$.

Estimation of HbA1c, GA and 1,5-AG from time in range

The least squares method was used to estimate HbA1c levels from $TIR^{70–180}$, $TAR^{>180}$ and $TBR^{<70}$ (Table 4; Figure 1a–c). The estimated HbA1c corresponding to a $TIR^{70–180}$ of 70% was 6.9% (95% confidence interval [CI] 6.5–7.2%) in type 1 diabetes mellitus patients, and 7.1% (95% CI 7.0–7.3%) in type 2 diabetes mellitus patients. The estimated HbA1c corresponding to a $TIR^{70–180}$ of 50% was 7.7% in both type 1 diabetes mellitus and type 2 diabetes mellitus patients. The estimated HbA1c corresponding to a $TAR^{>180}$ of 25% was 7.1% in both type 1 diabetes mellitus and type 2 diabetes mellitus patients. The estimated HbA1c corresponding to a $TBR^{<70}$ of 4% was 7.9% (95% CI 7.7–8.2%) in type 1 diabetes mellitus patients, and 7.1% (95% CI 6.9–7.2%) in type 2 diabetes mellitus patients.

Table 5 | Estimation of glycated albumin and 1,5-anhydro-D-glucitol from continuous glucose monitoring metrics

	Type 1 diabetes mellitus			Type 2 diabetes mellitus		
	GA (%)	95% CI	95% PI	GA (%)	95% CI	95% PI
$TIR^{70–180}$						
50%	23.7	(22.9–24.5)	(17.2–30.2)	21.4	(20.5–22.4)	(15.5–27.3)
70%	20.3	(19.0–21.7)	(13.8–26.9)	19.3	(18.7–19.9)	(13.5–25.1)
	$GA = 32.14 - 0.17 \times TIR^{70–180}$			$GA = 26.69 - 0.11 \times TIR^{70–180}$		
	$R = 0.65$, $R^2 = 0.42$, RMSE = 3.24			$R = 0.56$, $R^2 = 0.31$, RMSE = 2.92		
$TAR^{>180}$						
25%	21.3	(20.2–22.4)	(14.7–27.9)	19.2	(18.7–19.8)	(13.8–24.7)
50%	24.7	(23.9–25.5)	(18.1–31.3)	22.1	(21.2–23.1)	(16.6–27.6)
	$GA = 17.86 + 0.14 \times TAR^{>180}$			$GA = 16.37 + 0.11 \times TAR^{>180}$		
	$R = 0.64$, $R^2 = 0.41$, RMSE = 3.27			$R = 0.64$, $R^2 = 0.41$, RMSE = 2.71		
$TBR^{<70}$						
1%	25.2	(23.8–26.5)	(17.0–33.3)	19.3	(18.6–20.0)	(12.5–26.1)
4%	24.6	(23.5–25.6)	(16.4–32.7)	18.9	(18.3–19.6)	(12.2–25.7)
	$GA = 25.36 - 0.20 \times TBR^{<70}$			$GA = 19.41 - 0.12 \times TBR^{<70}$		
	$R = 0.31$, $R^2 = 0.10$, RMSE = 4.03			$R = 0.26$, $R^2 = 0.07$, RMSE = 3.40		
	Type 1 diabetes mellitus			Type 2 diabetes mellitus		
	1,5-AG (μg/mL)	95% CI	95% PI	1,5-AG (μg/mL)	95% CI	95% PI
$TIR^{70–180}$						
50%	4.3	(3.7–4.8)	(–0.3–8.8)	6.4	(4.8–8.1)	(–3.9–16.8)
70%	6.0	(5.1–6.9)	(1.4–10.6)	10.0	(9.0–11.0)	(–0.3–20.3)
	$1,5\text{-AG} = -0.03 + 0.09 \times TIR^{70–180}$			$1,5\text{-AG} = -2.46 + 0.18 \times TIR^{70–180}$		
	$R = 0.53$, $R^2 = 0.28$, RMSE = 2.25			$R = 0.54$, $R^2 = 0.29$, RMSE = 5.17		
$TAR^{>180}$						
25%	5.4	(4.7–6.2)	(0.8–10.1)	10.2	(9.1–11.3)	(–0.4–20.7)
50%	3.8	(3.2–4.3)	(–0.8–8.4)	6.2	(4.4–8.0)	(–4.4–16.9)
	$1,5\text{-AG} = 7.14 - 0.07 \times TAR^{>180}$			$1,5\text{-AG} = 14.18 - 0.16 \times TIR^{>180}$		
	$R = 0.51$, $R^2 = 0.26$, RMSE = 2.29			$R = 0.51$, $R^2 = 0.26$, RMSE = 5.29		

The least squares method was used to estimate glycated albumin (GA) and 1,5-anhydro-D-glucitol (1,5-AG) from time in range (TIR), time above range (TAR), and time below range (TBR). 95% CI, 95% confidence interval; 95% PI, 95% prediction interval; *R*, multiple correlation coefficient; R^2, coefficient of determination; RMSE, root mean square error; $TAR^{>180}$, time above range >180 mg/dL; $TBR^{<70}$, time below range <70 mg/dL; $TIR^{70–180}$, time in range 70–180 mg/dL.

Similar analyses were carried out to estimate GA levels (Table 5; Figure 1d–f). The estimated GA corresponding to a $TIR^{70–180}$ of 70% and 50% was 20.3% (95% CI 19.0–21.7%) and 23.7% (95% CI 22.9–24.5%) in type 1 diabetes mellitus patients, and 19.3% (95% CI 18.7–19.9%) and 21.4% (95% CI 20.5–22.4%) in type 2 diabetes mellitus patients, respectively. The estimated GA corresponding to a $TAR^{>180}$ of 25% was higher in type 1 diabetes mellitus patients (21.3, 95% CI 20.2–22.4%) than in type 2 diabetes mellitus patients (19.2%, 95% CI 18.7–19.8%). The estimated GA corresponding to a $TBR^{<70}$ of 4% was higher in type 1 diabetes mellitus (24.6%; 95% CI 23.5–25.6%) than in type 2 diabetes mellitus patients (18.9, (95% CI 18.3–19.6%).

The results of 1,5-AG are shown in Table 5 and Figure 2. The estimated 1,5-AG corresponding to a $TIR^{70–180}$ of 70% was as low as 6.0 μg/mL (95% CI 5.1–6.9 μg/mL) in type 1 diabetes mellitus patients. The estimated 1,5-AG corresponding to a $TAR^{>180}$ of 25% was also low in type 1 diabetes mellitus patients (5.4 μg/mL, 95% CI 4.7–6.2 μg/mL). 1,5-AG showed no significant single regression lines for estimating $TBR^{<70}$.

Estimation of time in range from HbA1c, GA and 1,5-AG

In type 1 diabetes mellitus patients and type 2 diabetes mellitus patients (Table 6), least squares regression models were used to assess the relationship between CGM metrics and HbA1c (Figure S1a–c). In type 1 diabetes mellitus patients, the estimated $TIR^{70–180}$ and $TAR^{>180}$ corresponding to an HbA1c level of 7.0% were 56.1% (95% CI 52.3–59.8%) and 35.2% (95% CI 30.7–39.7%), respectively. In type 2 diabetes mellitus patients, the estimated $TIR^{70–180}$ and $TAR^{>180}$ corresponding to an HbA1c level of 7.0% were 74.2% (95% CI 71.3–77.2%) and 21.4% (95% CI 18.8–24.0, respectively.

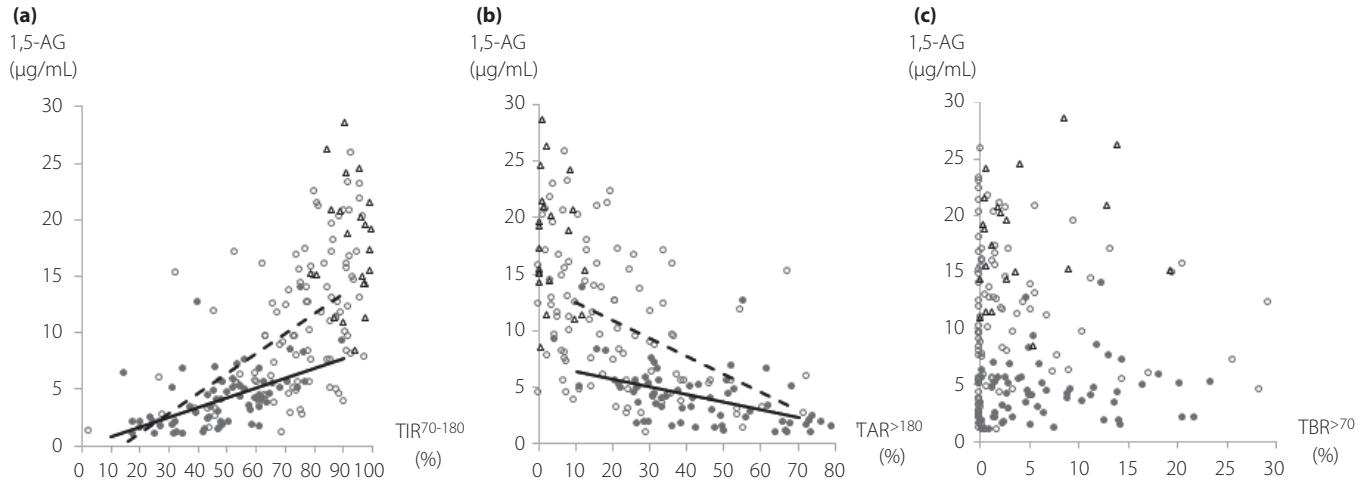

Figure 2 | Association of 1,5-anhydro-D-glucitol (1,5-AG) with time in range (TIR), time above range (TAR) and time below range (TBR). ●, Type 1 diabetes mellitus; ○, type 2 diabetes mellitus; Δ, impaired glucose tolerance; solid line, single regression line in type 1 diabetes mellitus patients; broken line, single regression lines in type 2 diabetes mellitus patients. (a) Association between 1,5-AG and $TIR^{70–180}$. (b) Association between 1,5-AG and $TAR^{>180}$. (c) Association between 1,5-AG and $TBR^{<70}$.

The estimated $TIR^{70–180}$ corresponding to a GA of 20% was 58.4% (95% CI 54.2–62.6%) in type 1 diabetes mellitus patients, and 70.4% (95% CI 67.2–73.6%) in type 2 diabetes mellitus patients (Figure S1d–f). The estimated $TIR^{70–180}$ corresponding to a 1,5-AG level of 10.0 μg/mL was 67.6% (95% CI 59.3–75.9%) in type 1 diabetes mellitus, and 72.5% (95% CI 69.4–75.7%) in type 2 diabetes mellitus patients (Figure S2a–c).

DISCUSSION

The present study investigated the relationship between CGM metrics, such as $TIR^{70–180}$, and glycemic control indicators, such as HbA1c, GA and 1,5-AG. The results of this study showed that $TIR^{70–180}$ was correlated with not only HbA1c, but also GA and 1,5-AG. We also found that the estimated HbA1c corresponding to a $TIR^{70–180}$ of 70% and a $TAR^{>180}$ of 25% was approximately 7% for both type 1 diabetes mellitus and type 2 diabetes mellitus patients, and that the estimated GA and 1,5-AG calculated from the TIR and TAR might be different between type 1 diabetes mellitus and type 2 diabetes mellitus patients.

Previous reports have shown that diabetic microvascular complications and vascular endothelial dysfunction are associated with $TIR^{70–180}$ deterioration[23–26]. The Advanced Technologies & Treatments for Diabetes stated that TIR is an appropriate and useful clinical target and outcome measurement that complements HbA1c for a wide range of patients with diabetes[21]. The Advanced Technologies & Treatments for Diabetes recommends a $TIR^{70–180}$ target of >70% for the management of most cases of type 1 diabetes mellitus and type 2 diabetes mellitus[21]. Beck *et al.*[27] reported that a $TIR^{70–180}$ of 70% corresponded to an HbA1c level of approximately 7%. Another analysis of randomized trials on type 1 diabetes mellitus and type 2 diabetes mellitus also reported that a $TIR^{70–180}$ of 70% corresponded to an HbA1c level of 6.7%[28]. In the present study, the HbA1c level corresponding to a $TIR^{70–180}$ of 70% was 6.9% in type 1 diabetes mellitus patients and 7.1% in type 2 diabetes mellitus patients, which was similar to those reported previously.

The GA corresponding to a $TIR^{70–180}$ of 70% and 50% was 20.5% and 23.8% in type 1 diabetes mellitus patients, and 19.3% and 21.5% in type 2 diabetes mellitus patients, respectively. GA has been reported to be more useful than HbA1c as a glycemic variability index, such as postprandial hyperglycemia[14–16]. In fact, it has been reported that GA is higher in type 1 diabetes mellitus patients than in type 2 diabetes mellitus patients, even when HbA1c is similar[29]. In addition, GA is known to be low in obese individuals[15]. In the present study, patients with type 1 diabetes mellitus had significantly lower BMI than those with type 2 diabetes mellitus. Thus, patients with type 1 diabetes mellitus were more unstable in terms of blood glucose variability and had a lower BMI than those with type 2 diabetes mellitus, suggesting that there was a significant difference between type 1 diabetes mellitus and type 2 diabetes mellitus patients in the single regression line with GA as the objective variable.

The 1,5-AG marker has been considered an indicator of postprandial glycemic control in patients with HbA1c levels of <8.0%[29–31]. Considering that 77.7% of the participants in the present study had HbA1c levels of <8.0%, a relationship between 1,5-AG and $TAR^{>180}$ might be assumed. In contrast, the present study showed that 1,5-AG corresponding to a $TIR^{70–180}$ of 70% was lower in patients with type 1 diabetes mellitus (6.0 μg/mL) than in those with type 2 diabetes mellitus (10.0 μg/mL). It has been reported that 1,5-AG might not be a

Table 6 | Estimation of time in range, time above range and time below range from glycemic control indicators in type 1 diabetes mellitus and type 2 diabetes mellitus patients

Type 1 diabetes mellitus	$TIR^{70–180}$ (%)			$TAR^{>180}$ (%)			$TBR^{<70}$ (%)		
	Estimate	95% CI	95% PI	Estimate	95% CI	95% PI	Estimate	95% CI	95% PI
HbA1c (%)									
6.0	66.1	(60.1–72.1)	(40.6–91.7)	22.8	(15.6–30.0)	(−7.9–53.5)	11.1	(8.1–14.0)	(−1.6–23.7)
7.0	56.1	(52.3–59.8)	(30.9–81.2)	35.2	(30.7–39.7)	(5.1–65.3)	8.7	(6.9–10.6)	(−3.7–21.1)
8.0	46.0	(42.9–49.1)	(20.9–71.1)	47.6	(43.9–51.4)	(17.6–77.6)	6.4	(4.8–7.9)	(−6.0–18.7)
	$TIR^{70–180}$ = 126.52 − 10.06 × HbA1c, RMSE = 12.46			$TAR^{>180}$ = −51.61 + 12.40 × HbA1c, RMSE = 14.92			$TBR^{<70}$ = 25.09 − 2.34 × HbA1c, RMSE = 6.14		
GA (%)									
16.0	68.3	(61.8–74.8)	(42.7–94.0)	20.8	(12.8–28.8)	(−10.6–52.2)	10.8	(7.6–14.1)	(−2.1–23.8)
20.0	58.4	(54.2–62.6)	(33.2–83.6)	32.7	(27.6–37.8)	(1.9–63.5)	8.9	(6.8–11.0)	(−3.8–21.6)
24.0	48.5	(45.4–51.5)	(23.5–73.5)	44.6	(40.9–48.3)	(14.0–75.2)	6.9	(5.4–8.5)	(−5.7–19.6)
	$TIR^{70–180}$ = 109.17 − 2.51 × GA, RMSE = 12.43			$TAR^{>180}$ = −26.73 + 2.97 × GA, RMSE = 15.20			$TBR^{<70}$ = 18.65 − 0.49 × GA, RMSE = 6.28		
1,5-AG (μg/mL)									
8.0	61.1	(55.1–67.2)	(32.8–89.4)	29.9	(22.5–37.3)	(−5.0–64.8)			
10.0	67.6	(59.3–75.9)	(38.7–96.5)	22.4	(12.1–32.6)	(−13.257.9)			
12.0	74.1	(63.4–84.8)	(44.5–103.7)	14.8	(1.6–28.1)	(−21.7–51.4)			
	$TIR^{70–180}$ = 35.15 + 3.25 × 1,5-AG, RMSE = 13.84			$TAR^{>180}$ = 60.04 − 3.77 × 1,5-AG, RMSE = 17.04					
Type 2 diabetes mellitus	$TIR^{70–180}$ (%)			$TAR^{>180}$ (%)			$TBR^{<70}$ (%)		
	Estimate	95% CI	95% PI	Estimate	95% CI	95% PI	Estimate	95% CI	95% PI
HbA1c (%)									
6.0	88.3	(83.493.2)	(58.3–118.3)	3.4	(−1.0–7.8)	(−23.4–30.1)	8.3	(5.9–10.7)	(−6.3–22.9)
7.0	74.2	(71.3–77.2)	(44.5–104.0)	21.4	(18.8–24.0)	(−5.1–47.9)	4.4	(2.9–5.8)	(−10.1–18.8)
8.0	60.2	(55.5–64.8)	(30.2–90.1)	39.4	(35.3–43.6)	(12.7–66.1)	0.4	(−1.–2.7)	(−10.0–10.5)
	$TIR^{70–180}$ = 172.70 − 14.07 × HbA1c, RMSE = 14.92			$TAR^{>180}$ = −104.74 + 18.02 × HbA1c, RMSE = 13.30			$TBR^{<70}$ = 32.00 − 3.95 × HbA1c, RMSE = 7.25		
GA (%)									
16.0	82.2	(78.2–86.2)	(51.3–113.2)	11.9	(8.0–15.8)	(−18.3–42.0)	5.9	(3.9–7.9)	(−9.4–21.2)
20.0	70.4	(67.2–73.6)	(39.5–101.3)	26.0	(22.9–29.2)	(−4.0–56.1)	3.6	(2.0–5.1)	(−11.7–18.8)
24.0	58.6	(53.1–64.0)	(27.4–89.7)	40.2	(34.9–45.5)	(9.8–70.6)	1.2	(−1.5–3.9)	(14.2–16.6)
	$TIR^{70–180}$ = 129.57 − 2.96 × GA, RMSE = 15.48			$TAR^{>180}$ = −44.83 + 3.54 × GA, RMSE = 15.07			$TBR^{<70}$ = 15.26 − 0.58 × HbA1c, RMSE = 7.63		
1,5-AG (μg/mL)									
8.0	69.3	(65.9–72.7)	(37.9–100.6)	26.5	(22.8–30.1)	(−7.2–60.1)			
10.0	72.5	(69.4–75.7)	(41.2–103.9)	23.2	(19.9–26.6)	(−10.4–56.9)			
12.0	75.8	(72.6–79.0)	(44.5–107.1)	20.0	(16.6–23.4)	(−13.6–53.6)			
	$TIR^{70–180}$ = 56.12 + 1.64 × 1,5-AG, RMSE = 15.70			$TAR^{>180}$ = 39.44 − 1.62 × 1,5-AG, RMSE = 16.86					

The least squares method was used to predict from time in range (TIR) and time above range (TAR) from hemoglobin A1c (HbA1c), glycated albumin (GA), and 1,5-anhydro-D-glucitol (1,5-AG). 95% CI, 95% confidence interval; 95% PI, 95% prediction interval; RMSE, root mean square error; $TAR^{>180}$, time above range >180 mg/dL; $TBR^{<70}$, time below range <70 mg/dL; $TIR^{70–180}$, time in range 70–180 mg/dL.

useful glycemic control indicator in patients with poor glycemic control[30–33]. It has been also reported that patients with type 1 diabetes mellitus have lower 1,5-AG levels than those with type 2 diabetes mellitus[32]. For these reasons, there seemed to be a difference in the regression equation using 1,5-AG as an objective variable between type 1 diabetes mellitus and type 2 diabetes mellitus patients.

Beck *et al.*[26] reported that an HbA1c level of 7.0% corresponded to a $TIR^{70–180}$ of 64% in patients with type 1 diabetes mellitus. The present study found that an HbA1c level of 7.0%

corresponded to a $TIR^{70–180}$ of 56.1% in patients with type 1 diabetes mellitus. Furthermore, Urakami *et al.*[34] reported that an HbA1c level of 7.0% corresponded to a $TIR^{70–180}$ of 55.1% in Japanese children and adolescents with type 1 diabetes mellitus, a finding similar to that presented in the present study. In contrast, we found that an HbA1c level of 7.0% corresponded to a $TIR^{70–180}$ of 74.2% in patients with type 2 diabetes mellitus, which differed from the values of those with type 1 diabetes mellitus. Patients with type 1 diabetes mellitus have been known to have more frequent blood glucose fluctuations than those with type 2 diabetes mellitus[8]. Given that HbA1c was higher and $TIR^{70–180}$ was lower in patients with type 1 diabetes mellitus than in those with type 2 diabetes mellitus, there might have been differences in single regression lines. Thus, the present results suggest that the $TIR^{70–180}$ estimated from HbA1c might be different between patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus. Therefore, $TIR^{70–180}$ targets should be set individually, considering various factors, such as the type of diabetes, types of diabetes therapy and risk for hypoglycemia[21].

The present study had certain limitations. First, this was an observational study carried out at a single institution. Second, there is an issue of measurement accuracy of CGM. It is known that the mean absolute relative difference of FreeStyle Libre Pro® is 11.1%[35]. However, it has been reported that CGM might overestimate hypoglycemia[36–38]. In fact, 40.9% of patients with IGT not receiving oral antidiabetics had $TBR^{<70}$ of ≥4%. Therefore, it might be necessary to evaluate the accuracy of CGM measurements through self-monitoring of blood glucose, which should be considered in future studies. Third, HbA1c, GA and 1,5-AG were measured at only one timepoint, on the day of CGM application. There is the possibility of a deviation between CGM metrics, such as TIR, and glycemic control indicators, such as HbA1c, when the glycemic control is improved over a short period. Therefore, it is desirable to measure glycemic control indices (such as HbA1c) multiple times, and further investigation should be necessary. Last, given that the present study used 14 days of retrospective CGM, long-term studies using real-time CGM or intermittently scanned CGM will be necessary in the future.

In conclusion, the present study found that $TIR^{70–180}$ was associated with not only HbA1c, but also GA and 1,5-AG. We also found that the estimated HbA1c corresponding to a TIR of 70% and a $TAR^{>180}$ of 25% was similar between patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus, and that the estimated GA and the estimated 1,5-AG calculated from TIR and TAR might be different between patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Relationships between time in range and patient background.
Figure S1 | Single regression lines with time in range (TIR), time above range (TAR) and time below range (TBR) as the objective variables, and hemoglobin A1c (HbA1c) and glycated albumin (GA) as the explanatory variables.
Figure S2 | Single regression lines with time in range (TIR), time above range (TAR) and time below range (TBR) as the objective variables and 1,5-anhydro-D-glucitol (1,5-AG) as the explanatory variable.