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The Optimal "Time in Range" and "Time below Range" are Difficult to Coordinate in Patients with Type 1 Diabetes

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Achieving the optimal glucose level time in range (TIR), as recently proposed by the "International Consensus on Time in Range," is challenging. We retrospectively analyzed data from 192 patients, including 58 with type 1 diabetes, using the FreeStyle Libre Pro system. This device was used by physicians for continuous glucose monitoring (CGM) and for making therapeutic decisions based on unbiased data, as the patients were blinded to their blood glucose levels during monitoring. The desired 70% TIR among patients with type 2 diabetes corresponded to an HbA1c of 7.7%. Importantly, however, a 70% TIR for patients with type 1 diabetes corresponded to an HbA1c of 6.9%, which diverged markedly from the HbA1c of 7.9% that corresponded to the desired 4% time below range (TBR). Moreover, these dissociations were observed more in patients with type 1 diabetes with a higher % coefficient of variation (> 36%). Hence, while the TIR is strongly correlated with HbA1c, it is difficult to coordinate with the TBR in Japanese patients with type 1 diabetes. As these metrics (which are critical indicators in clinical practice) are rapidly gaining popularity globally, including in Japan, our data strongly support the cautious use of new CGM metrics such as TIR and TBR/time above range, and emphasize the importance of individualized treatment in achieving the optimal TIR and TBR, especially in patients with type 1 diabetes.

Keywords: continuous glucose monitoring; diabetes mellitus; time above range; time below range; time in range
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Introduction

Continuous glucose monitoring (CGM) can be performed both professionally and personally (Bode et al. 1999; Rodbard 2016; Vigersky and Shrivastav 2017). While professional type CGM is performed by physicians, who use it to make therapeutic decisions based on unbiased data given that patients are blinded to their blood glucose levels during monitoring, personal type CGM is conducted by patients who can measure their blood glucose levels in real-time and respond accordingly by adjusting the amounts of injected insulin and/or making changes in lifestyle habits (Bode et al. 1999; Rodbard 2016; Vigersky and Shrivastav 2017).

The International Consensus on Time in Range (TIR) recently proposed that the percentages of TIR, time below range (TBR), and time above range (TAR) should be considered as key CGM metrics for short-term glycemic control (Urakami et al. 2020). Since these metrics have rapidly spread worldwide (including in Japan) and are used as critical indicators in clinical practice, they should be re-verified for clinical use. Importantly, few studies involving the simultaneous analyses of TIR, TBR, and TAR have been published. Therefore, in this study, we aimed to investigate the relationships between TIR, TBR, and TAR, as measured during professional CGM among patients with diabetes.

Materials and Methods

Ethics statement

This study was approved by the Gunma University Institutional Review Board, and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Each patient provided written informed consent before undergoing any study-related pro-

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cedures.

Patients

All patients with type 1 and type 2 diabetes who used the FreeStyle Libre Pro® device (Abbot Japan, Tokyo, Japan) at the Department of Internal Medicine, Division of Endocrinology and Diabetes, Gunma University Hospital between 2017 and 2019 were reviewed. Those who wore the device for at least 9 days were included given that previous reports showed a correlation between HbA1c and mean sensor glucose values (Xing et al. 2011). The exclusion criteria were: patients treated with glucocorticoids, those who were anemic (hematocrit < 39% in men and < 36% in women), and those with compromised glucose levels (such as pregnant women). In addition to patients with anemia, those treated with iron or erythropoietin preparations were also excluded. The included patients' baseline characteristics are shown in Table 1.

Glycemia assessment

The patients' glucose levels were measured using the FreeStyle Libre Pro device every 15 min for up to 14 days. Patients were advised to continue their normal daily routines. The results from the CGM were downloaded to the FreeStyle Libre Pro web-based software (Abbot), and the proportions of time when glucose values were between 70

Table 1. Patient Characteristics.

	Type 1 diabetes	Type 2 diabetes
N (male/female)	58 (18/40)	134 (61/73)
Age (years)	43.8 ± 3.4	62.8 ± 2.3
Body mass index (kg/m^2)	23.4 ± 1.0	25.1 ± 0.9
Plasma glucose (mg/dL)	177.8 ± 18.6	164.2 ± 11.7
HbA1c (%)	7.7 ± 0.3	7.9 ± 0.2
Serum C-peptide (ng/mL)	0.33 ± 0.2	1.9 ± 0.37
C-peptide index	0.19 ± 0.1	1.19 ± 0.18
eGFR (mL/min/1.73 m^2)	90.4 ± 5.4	74.1 ± 4.5
eGFR < 60 (%)	11.1	26.5
Diabetic retinopathy (%)	32.6	50.1
Anti-diabetic medication		
Sulfonylurea/glinide (%)	0	25
Dipeptidyl peptidase-4 inhibitor (%)	0	27.6
Sodium glucose cotransporter 2 (%)	0	30.6
Metformin (%)	0	35.1
Glucagon like peptide-1 receptor agonist (%)	0	20.1
Insulin		
Continuous subcutaneous insulin infusion (not including Sensor Augmented Pump) (%)	30.6	1.5
Multiple daily injections (%)	64.5	44
Conventional insulin therapy (%)	3.2	24.6
Mean glucose (mg/dL)	167 ± 9.4	160 ± 6.9
eHbA1c (%)	7.5 ± 0.3	7.2 ± 0.2
TIR (%)	52.6 ± 3.9	66.1 ± 3.5
TBR (< 70) (%)	8.9 ± 2.1	5.6 ± 0.95
TBR (< 54) (%)	4.0 ± 1.2	0.68 ± 0.34
TAR (> 180) (%)	38.5 ± 4.7	30.9 ± 3.7
TAR (> 250) (%)	14.8 ± 3.5	14.4 ± 2.4
SD glucose (mg/dL)	69.0 ± 4.1	49.9 ± 3.0
% CV (%)	42.0 ± 2.1	31.1 ± 7.2
MAGE (mg/dL)	149 ± 8.4	112 ± 5.7
ADRR (mmol/l)	32.3 ± 3.1	25.0 ± 2.2

Data are shown as mean ± SD, or the percentage (%).
HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; TIR, time in range; TBR, time below range; TAR, time above range; % CV, % coefficient of variation; MAGE, mean amplitude of glycemic excursions; ADRR, average daily risk range.

and 180 mg/dL (i.e., the TIR), below 70 mg/dL (the TBR), and above 180 mg/dL (the TAR) were calculated. We performed the analyses except on days 0-1 and 13-14, when the mean absolute relative difference is typically high (Tsoukas et al. 2020). HbA1c was measured within 1 month after CGM.

Statistics

All results are expressed as means ± standard deviations for continuous variables and as absolute numbers with relative percentages for categorical variables. The associations between HbA1c levels and each of TIR, TBR, and TAR were assessed using Pearson's product-moment correlation coefficients. Point estimates and 95% confidence intervals (CIs) of HbA1c values that corresponded to TIRs of 70%, TBRs of 4%, and TARs of 25% were calculated using simple linear regression models. All tests for significance and resulting p-values were 2-sided, and the significance level was 0.05. Statistical analyses were performed using JMP 9.0.2 (SAS Institute, Cary, NC, USA).

Results

The TIR was strongly correlated with HbA1c in all patients with diabetes (R = 0.593, $p < 0.0001$) (Fig. 1A). While the TBR was mildly but significantly correlated with HbA1c (R = 0.309, $p < 0.0001$) (Fig. 1B), the TAR was more highly correlated (R = 0.666, $p < 0.0001$) (Fig. 1C). To achieve a recommended 70% TIR, HbA1c was required to be approximately 7.6% (95% CI 7.4-7.7%) (Fig. 1A), which was slightly inconsistent with previously published data showing that a 70% TIR corresponded to an HbA1c of approximately 7.0% (Nathan et al. 2008; Urakami et al. 2020). To achieve a TBR and TAR of 4% and 25%, respectively (as recommended), the HbA1c values were required to be approximately 7.9% (95% CI 7.7-8.0%) and 7.5% (95% CI 7.4-7.6%), respectively (Fig. 1B, C). Similar results were observed in patients with type 2 diabetes, in whom HbA1c was strongly correlated with TIR (R = 0.658, $p < 0.0001$) (Fig. 1D), less so with TBR (R = 0.325, $p = 0.0003$) (Fig. 1E), and strongly with TAR (R = 0.686, $p < 0.0001$) (Fig. 1F). To achieve an appropriate TIR, TBR, and TAR, the HbA1c needed to be approximately 7.6-7.7 % (Fig. 1D, E, F). While a similar result was also observed in patients with type 1 diabetes in that HbA1c was strongly correlated with TIR (R = 0.660, $p < 0.0001$) (Fig. 2A), less so with TBR (R = 0.327, $p = 0.0122$) (Fig. 2B), and strongly with TAR (R = 0.692, $p < 0.0001$) (Fig. 2C), there was a large difference in the levels of HbA1c required to achieve the recommended TIR and TBR. Moreover, these discordances were more readily observed in patients with type 1 diabetes with higher % coefficients of variation (> 36 %) (Fig. 2D, E, F) (Danne et al. 2017). These data demonstrated the challenge of achieving a 70% TIR simultaneously with a 4% TBR in patients with type 1 diabetes, since they tend to have higher glycemic variability (GV). In this regard, insulin pump therapy could lower HbA1c and GV, and it has been reported to influence the TIR (Battelino et al. 2019; Urakami et al. 2020). Therefore, we also investigated patients on insulin pump therapy alone. The analysis may have been underpowered since the number of patients on insulin pump therapy was small (n = 19), but HbA1c and % coefficients of variation did not significantly differ between patients on insulin pump therapy and multiple daily injections in this study (7.5 ± 0.2 vs. 7.8 ± 0.2, $p = 0.208$; and 42.4 ± 1.6 vs. 41.8 ± 1.5, $p = 0.408$, respectively) (data not shown). Thus, there was a smaller difference in HbA1c levels required to achieve the recommended TIR and TBR in patients with insulin pump therapy than in patients with type 1 diabetes with higher % coefficients of variation, demonstrating that these discordances could be due to the high GV rather than the treatment itself (Fig. 3A, B, C).

Discussion

Our data derived from professional CGM demonstrated that achieving 70% TIR required an HbA1c level of 6.9%, while a 4% TBR required it to be approximately 7.9%; this indicated the difficulty inherent in obtaining a 70% TIR while avoiding hypoglycemia in patients with type 1 diabetes.

A good correlation has previously been reported between HbA1c and TIR among a broad range of individuals, including those of different ages and those using various insulin control technologies. HbA1c has been used as an index of blood glucose control in the past few years; therefore, the correlations between sensor glucose values and HbA1c could be affected by various factors (such as undergoing treatment) during this period (Rodbard 2016; Urakami et al. 2020). In this regard, our data are consistent with those of previous studies, thereby supporting our analyses (especially those comparing type 1 and type 2 diabetes given that the methodology was the same) (Nathan et al. 2008; Urakami et al. 2020).

An HbA1c of 7.0%, which is recognized as the target level required for preventing microvascular complications, reportedly corresponds to a 70% TIR (Nathan et al. 2008; Urakami et al. 2020); however, the 95% CIs for the predicted HbA1c values are reportedly very broad (Vigersky and McMahon 2019; Rodbard 2020; Urakami et al. 2020). For example, one study found that the HbA1c would have to be 5.6-8.3% for a 70% TIR, given the wide 95% CI (Nathan et al. 2008). In this regard, our patients' data were tighter since the 95% CI was relatively narrow (7.4-7.7% for a TIR of 70%) despite corresponding to a higher HbA1c. This may be attributable to the small sample size and to the fact that our patients used professional CGM, which may have helped to produce non-biased data owing to its blinded nature.

Recent studies showed that HbA1c and TIR were correlated; however, few previous studies investigated the correlation between HbA1c and TBR (Nathan et al. 2008; Vigersky and McMahon 2019; Urakami et al. 2020), and fewer still compared the correlation between HbA1c and

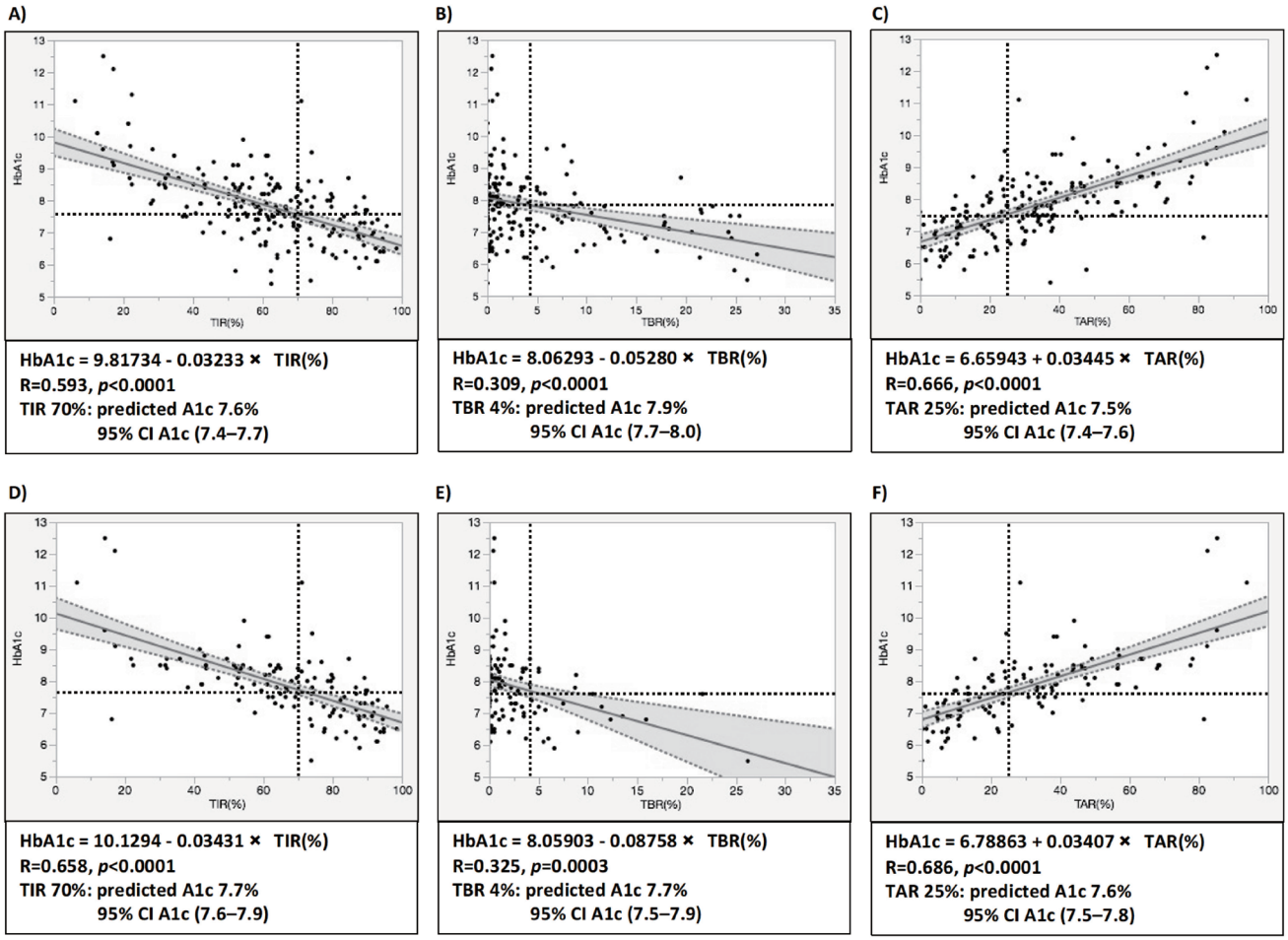

Fig. 1. Correlations between HbA1c and each of TIR (%) (A, D), TBR (%) (B, E), and TAR (%) (C, F).
A, B, C: In all patients with diabetes (n = 192). D, E, F: In patients with type 2 diabetes (n = 134).
CI, confidence interval; HbA1c, glycated hemoglobin; TAR, time above range; TBR, time below range; TIR, time in range.

both TIR and TBR simultaneously. Indeed, to avoid hypoglycemia and maintain a good quality of life (which involves achieving a TBR < 4%), HbA1c needed to be approximately 8.0%. This was inconsistent with the HbA1c level corresponding to a 70% TIR, indicating the difficulty in achieving a 70% TIR without hypoglycemia in patients with type 1 diabetes in this study. This might be due to higher GV, standard deviation, % coefficient of variation, mean amplitude of glycemic excursion, and average daily risk range in the type 1 diabetes group in this study, which highlighted the difficulty and importance of targeting GV in type 1 diabetes if the recommended targets are to be achieved safely (Irace et al. 2020; Rodbard 2020). Indeed, our data demonstrated that dissociations between the desired TIR and TBR were observed more frequently in patients with type 1 diabetes who had % coefficients of variation > 36%. In this regard, insulin pump therapy could lower both HbA1c and GV without causing hypoglycemia, and it has been reported that such therapy influences the TIR (Battelino et al. 2019; Urakami et al. 2020). However, 30% of the patients with type 1 diabetes in our study used insulin pump therapy; yet, it remained difficult for them to achieve the recommended TIR without experiencing hypoglycemia. Moreover, even though the number of patients on insulin pump therapy was very small in our study, they showed equivalent overall findings to those with type 1 diabetes (Fig. 2A, B, C vs. Fig. 3A, B, C), and these discordances were less readily observed in patients with type 1 diabetes with higher % coefficients of variation (> 36%) (Fig. 2D, E, F vs. Fig. 3A, B, C). This suggests that these discordances could be due to the high GV rather than the treatment itself (Fig. 3A, B, C). Further studies of patients' self-care habits, such as blood glucose testing frequency, bolus frequency, and carbohydrate counting, will be required to provide a better perspective of these data, as such habits are likely to influence the GV of individuals with type 1 diabetes.

It has been reported that the efficacy and accuracy of the FreeStyle Libre Pro device are high for patients with type 1 diabetes (Bailey et al. 2015); however, it has also been shown that CGM may not be accurate if GV is excessively high (Moser et al. 2019). Therefore, our data might

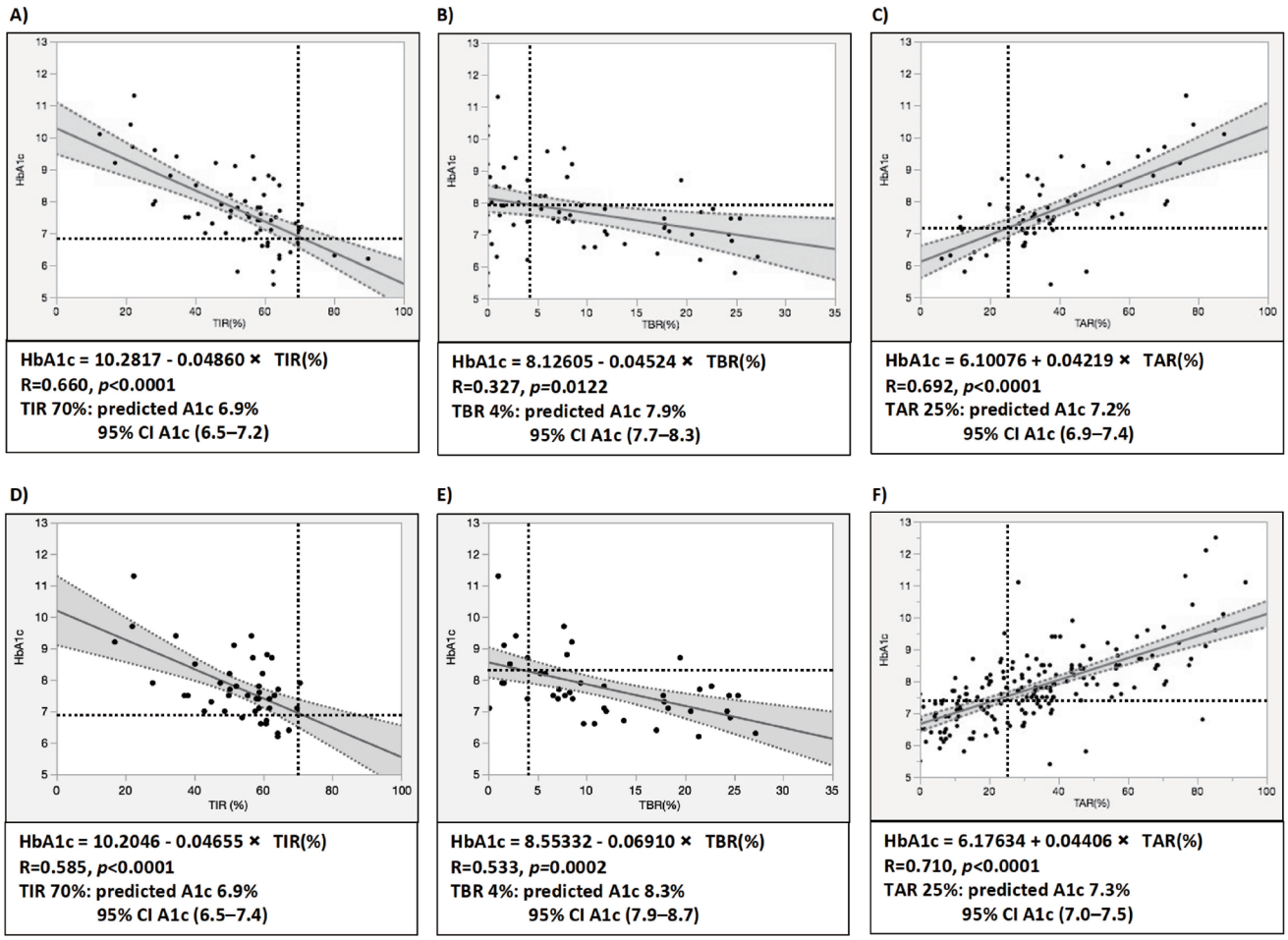

Fig. 2. Correlations between HbA1c and each of TIR (%) (A, D), TBR (%) (B, E), and TAR (%) (C, F).
A, B, C: In patients with type 1 diabetes (n = 58). D, E, F: In patients with type 1 diabetes who have a % coefficient of variation > 36% (n = 43).
CI, confidence interval; HbA1c, glycated hemoglobin; TAR, time above range; TBR, time below range; TIR, time in range.

be influenced by the glucose fluctuations in patients with type 1 diabetes. Moreover, other studies suggested that the accuracy of the FreeStyle Libre Pro system might not be reliable in the hypoglycemic range (Bailey et al. 2015). Indeed, the TBR (< 70) of patients with type 2 diabetes in our study was very high at 5.6%, but most patients did not feel hypoglycemic. This would explain the higher-than-expected HbA1c for a TIR of 70% (7.6%) than the 6.9% measured in a previous study (Irace et al. 2020). In this regard, the accuracy of readings below the hypoglycemic range was not confirmed in our study given that the FreeStyle Libre Pro does not utilize blood glucose for calibration. This issue is quite important not only for interpreting our own data but also the clinical finding of hypoglycemia unawareness. Indeed, the TBR (< 70) of patients with type 2 diabetes with multiple daily injections who were at risk of hypoglycemia in our study was also high at 4.0% (data not shown), but these patients did not feel hypoglycemic either. Further analyses using other CGM devices, such as Dexcom, would be necessary to confirm our data and detecting the unconsciousness of hypoglycemia.

Several limitations should be considered when interpreting our findings. First, 10-14-day CGM may not represent the true 90-day glycemia, since an individual's HbA1c reflects the average glycemia of the previous 90 days. Indeed, the estimated HbA1c value [calculated based on the ADAG study (Nathan et al. 2008)] and the true HbA1c value were different, especially in patients with type 2 diabetes (Table 1). Hence, the underlying GV of the individual may play a role (Fabris et al. 2020; Lu et al. 2020; Rama Chandran et al. 2020). Another reason might be that these values were obtained from a Caucasian cohort, and might not be completely applicable to our Japanese cohort given possible differences in genetic backgrounds. Moreover, the estimated HbA1c per the ADAG study was calculated based on repeated average glucose level measurements over 3 months (Nathan et al. 2008). In this study, we collected CGM data over ≥ 9 days because we used FreeStyle Libre Pro, which can only be used for 14 days and also provides unreliable data on days 0-1 and 13-14 when the mean abso-

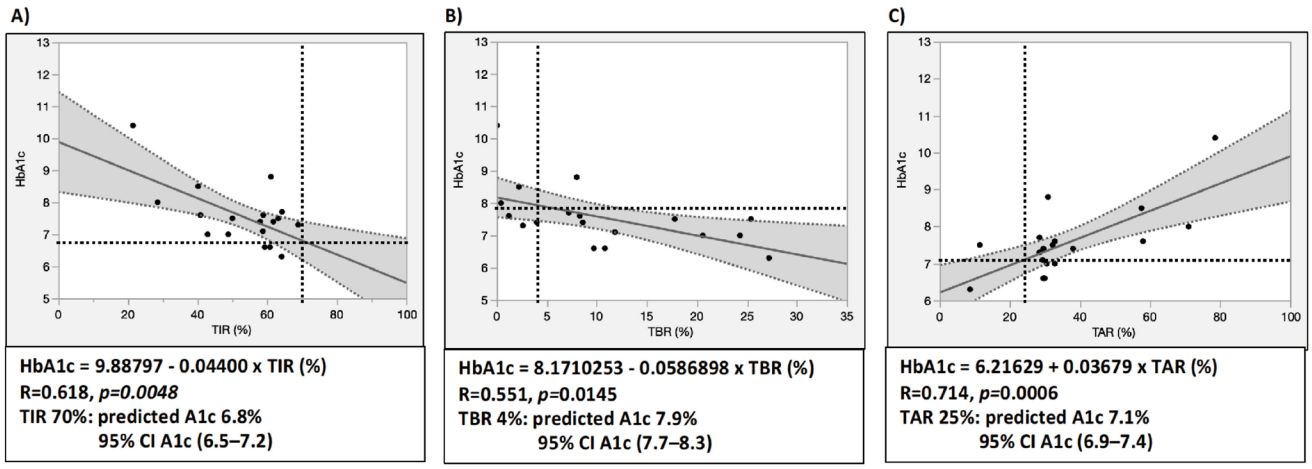

Fig. 3. Correlations between HbA1c and each of TIR (%) (A), TBR (%) (B), and TAR (%) (C) in patients with insulin pump therapy (n = 19).
CI, confidence interval; HbA1c, glycated hemoglobin; TAR, time above range; TBR, time below range; TIR, time in range.

lute relative difference is typically high; previous investigators recommended 12-15 days of CGM data (Xing et al. 2011). However, when we analyzed data from individuals who wore CGM for 14 days, our data remained concordant, thereby confirming our findings (data not shown).

This study was of a cross-sectional retrospective design with small sample size, and we evaluated Japanese patients only at our hospital. Notably, since TIRs < 70% for patients with type 1 diabetes were limited, all these data were predictions obtained by regression analyses. In this regard, a recent study produced similar findings, although they focused on the association between TIR and glycemic control indicators, such as HbA1c, glycated albumin, and 1,5-anhydro-D-glucitol, rather than the association between TIR and TBR (Ohigashi et al. 2021). Interestingly, they reported that to achieve the recommended TIR and TAR of 70% and 25%, respectively, the HbA1c values were required to be approximately 6.9% and 7.1%, respectively. However, achieving a TBR of 4% in patients with type 1 diabetes required the HbA1c value to be approximately 7.9%; this was quite similar to our findings (Ohigashi et al. 2021).

In summary, our investigation demonstrated that achieving a 70% TIR without hypoglycemia is challenging for patients with type 1 diabetes, indicating that efforts to achieve TIR could potentially lead to life-threatening hypoglycemia. Similarly, insufficient treatments for patients whose TIR and HbA1c levels have been underestimated could also lead to the deterioration of health with possible chronic or acute complications. While these critical indicators are rapidly spreading throughout clinical practices globally, including in Japan, our data strongly promote the cautious use of new CGM metrics such as TIR and TBR/TAR, and assert the importance of individualized treatment in achieving the optimal TIR and TBR, especially in patients with type 1 diabetes.

Conflict of Interest

The authors declare no conflict of interest.

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