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Exploring the inter-subject variability in the relationship between glucose monitoring metrics and glycated hemoglobin for pediatric patients with type 1 diabetes

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Abstract

Objectives: Despite the widespread diffusion of continuous glucose monitoring (CGM) systems, which includes both real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), an effective application of CGM technology in clinical practice is still limited. The study aimed to investigate the relationship between isCGM-derived glycemic metrics and glycated hemoglobin (HbA1c), identifying overall CGM targets and exploring the inter-subject variability.

Methods: A group of 27 children and adolescents with type 1 diabetes under multiple daily injection insulin-therapy was enrolled. All participants used the isCGM Abbott's FreeStyle Libre system on average for eight months, and clinical data were collected from the Advanced Intelligent Distant-Glucose Monitoring platform. Starting from each HbA1c exam date, windows of past 30, 60, and 90 days were considered to compute several CGM metrics. The relationships between HbA1c and each metric were explored through linear mixed models, adopting an HbA1c target of 7%.

Results: Time in Range and Time in Target Range show a negative relationship with HbA1c (R^2>0.88) whereas Time Above Range and Time Severely Above Range show a positive relationship (R^2>0.75). Focusing on Time in Range in 30-day windows, random effect represented by the patient's specific intercept reveals a high variability compared to the overall population intercept.

Conclusions: This study confirms the relationship between several CGM metrics and HbA1c; it also highlights the importance of an individualized interpretation of the CGM data.

Keywords: children; continuous glucose monitoring; HbA1c; regression analysis; time in range; type 1 diabetes.

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Introduction

Type 1 diabetes (T1D) is one of the most common chronic autoimmune diseases in childhood, characterized by insulin deficiency and resultant hyperglycemia [1–3]. Controlling glycemia remains key to prevent complications in this condition. According to the Diabetes Control and Complications Trial (DCCT), a closed relationship between hyperglycemia, glycated hemoglobin (HbA1c) and microvascular complications has been reported in patients with T1D [4, 5]. HbA1c is the gold standard indirect measure of glycemic control and it estimates the glycemic exposure over the last three months before sampling. However, this glucose metric, if used alone, may be insufficient to

optimize and personalize the therapy changes [6] because glucose levels can undergo large fluctuations secondary to daily activities. Indeed, HbA1c is inadequate to reveal the extent or timing of hypoglycemia, hyperglycemia, and glucose variability patterns. Moreover, certain conditions such as anemia, hemoglobinopathies, and iron deficiency can confound HbA1c measurements [6].

Continuous glucose monitoring (CGM), which includes both real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), can help in the assessment of glycemic control. Although both categories of monitoring systems provide information about glucose levels using interstitial subcutaneous fluid sensing technologies, the isCGM devices require a scanner to periodically collect glucose readings from the sensor whereas the rtCGM devices return glucose readings continuously and alert users to hypoglycemia and hyperglycemia in real-time [7]. Compared to the fingerstick blood glucose testing, CGM offers a larger amount of data and it is an effective tool to treat children and adolescents with T1D [8–10].

Additionally, CGM can retrospectively support diabetes management with an analysis of glucose metrics and patterns, including average glucose, time in range, time in hypoglycemia, time in hyperglycemia, and glucose variability. However, a systematic approach to CGM data evaluation is not yet adopted [7–10]. In the literature, each uses different components and some use different definitions for measuring the same component, thus it is difficult to select the adequate composite metric or the optimal scaling ranges.

The investigation of new or individualized clinical CGM targets to supplement the currently agreed-upon metrics for CGM-derived times in glucose ranges may be helpful for clinicians, researchers, and patients to use and interpret CGM data in clinical care and research [10, 11]. In the present study, we analyzed the relationship between the isCGM-derived glycemic metrics and the corresponding HbA1c levels on a group of 27 pediatric patients with T1D. Moreover, considering that many patients had multiple HbA1c measurements, we used linear mixed models to explore the inter-subject variability.

Materials and methods

Subjects

The clinical data analyzed in this study were collected in a real-world pilot study using the Advanced Intelligent Distant-Glucose Monitoring (AID-GM) platform [12] over a period of approximately 25 months between January 2018 and February 2020. The project was carried out jointly by the Pediatric Diabetology outpatient service of IRCCS Policlinico San Matteo Hospital in Pavia, Italy, and the Department of Electrical, Computer, and Biomedical Engineering of the University of Pavia. AID-GM is a web application that allows diabetic patients and their clinicians to easily share and inspect glucose monitoring data, to support metabolic control and therapeutic prescription adherence. A group of 27 young patients with T1D under multiple daily injection insulin-therapy, already being followed by the pediatric diabetes team and already using an isCGM system, were asked to periodically upload their glucose data through the application, with the help of their caregivers. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Fondazione IRCCS Policlinico San Matteo Hospital in Pavia, Italy (code number 20180056724). Childs' caregivers (or subjects aged ≥18 years) gave written informed consent for inclusion in the study.

Measurements

The isCGM system used in the study is the flash glucose monitoring FreeStyle Libre (Abbott Diabetes Care, Alameda, California, USA) [13]. Compared to rtCGM systems, the FreeStyle Libre has the advantage of factory calibration, a long sensor life of 14 days, and a simpler and more economic technology [14]. Additionally, a recent study has demonstrated the accuracy, safety, and user acceptability of the FreeStyle Libre system specifically in the pediatric population [15]. The FreeStyle Libre sensor measures interstitial glucose levels every minute and stores a reading (in a glucose range of 40–500 mg/dL) every 15 min in a rolling 8-h memory. This means that if a patient swipes the reader over the sensor at least every 8 h, no information is lost and 96 automatic measurements per day are stored. All sensor readings were performed with the same version of the FreeStyle Libre reader [13].

HbA1c in blood samples was measured by an ion-exchange HPLC single-cartridge Variant II method (Bio-Rad, Hercules, California, USA) for automated separation and determination of HbA1c, with a normal range of 4.5–6.2% in National Glycohemoglobin Standardization Program (NGSP) units. The intra- and inter-assay coefficients of variation were 0.62 and 2.08% at an HbA1c concentration of 8.0%. HbA1c was performed on average every 3.04 months (±0.51 standard deviation).

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends an HbA1c target of 7% for children, adolescents, and young adults aged ≤25 years who have access to comprehensive care, i.e., with access to analog insulins, advanced insulin delivery technology, and the ability to regularly check blood glucose and/or use CGM [16]. The condition of comprehensive care availability was verified for all the participants.

Data analysis

Starting from each HbA1c exam date, windows of past 30, 60, and 90 days were considered, and several CGM metrics were computed. Subsequently, the relationship between HbA1c and each metric was investigated. In agreement with the Advanced Technologies & Treatments for Diabetes (ATTD) consensus recommendations for CGM data usage [11], a window was considered valid if at least 70% of glucose measurements were available. The most useful metrics in clinical practice were selected, such as:

– Average glucose (mg/dL)

- Glucose Standard Deviation (SD) (mg/dL)
- Coefficient of Variation (CV: percent ratio between glucose standard deviation and average glucose, with a target ≤36%)
- Time in Range (TIR: percentage of glucose readings in the range 70–180 mg/dL)
- Time in Target Range (TIT: percentage of glucose readings in the range 70–140 mg/dL)
- Time Below Range (TBR: percentage of glucose readings below 70 mg/dL), which can be further divided into Time slightly Below Range (TBR_Lev1: percentage of glucose readings in the range 54–69 mg/dL), and Time severely Below Range (TBR_Lev1: percentage of glucose readings below 54 mg/dL)
- Time Above Range (TAR: percentage of glucose readings above 180 mg/dL), which can be further divided into Time slightly Above Range (TAR_Lev1: percentage of glucose readings in the range 181–250 mg/dL), and Time severely Above Range (TAR_Lev2: percentage of glucose readings above 250 mg/dL) [11]

The dataset revealed clusters of not-independent observational units because multiple HbA1c measurements were considered for each patient, when available. Therefore, the relationships between HbA1c and CGM metrics were explored through a linear mixed model [17], incorporating both fixed and random effects, as shown in Eq. (1) for a single patient and a generic glycemic metric:

$$\text{HbA1c} = b_{\text{pat}} + b_{\text{gly}} \cdots \text{glycemic\_metric} + e \quad (1)$$

More precisely, the patient-specific intercept b_{pat} represents the random effect, as each patient may have a specific effect added to the overall estimated intercept, whereas the glycemic metric coefficient b_{gly} is the fixed effect common to all patients, as in standard regression. Every CGM metric was used as a predictor to build separate HbA1c linear mixed models. For each linear mixed model, the compliance of the prediction errors e-distribution with the normality assumption is checked both by Shapiro-Wilk's statistical test (under the null hypothesis that the population is normally distributed) setting the significance threshold to 0.05 and by visual inspection of quantile-quantile plots. The variance explained by the entire mixed effects model is expressed by the conditional coefficient of determination R^2 on a 0–1 scale, calculated according to Eq. (2):

$$R^2 = \left(\sigma_r^2 + \sigma_f^2\right) / \left(\sigma_r^2 + \sigma_f^2 + \sigma_e^2\right), \quad (2)$$

where σ_r is the random effects variance, σ_f is the fixed effect variance, and σ_e is the observation-level variance [18, 19]. All the analyses were performed using the R system for statistical computing, version 3.5.1. Linear mixed model regression was implemented with the function "lme" available in the R package called "nlme" [20].

Results

As instructed, all the participants changed their FreeStyle Libre sensors every 14 days. Of the 27 patients originally considered for this study, four were discarded for not meeting the 70%-data availability requirement with any window width, as shown in Table 1. Not surprisingly, the longer the monitoring period becomes, the fewer valid windows there are, and the number of patients with valid data decreases to 21 and 18 when considering monitoring windows of 60 and 90 days, respectively. Anyway, there is no significant difference between the median HbA1c values, which are 7.35, 7.30, and 7.25 in NGSP units, considering accepted windows of 30, 60, and 90 days. In addition, it is possible to notice that the median HbA1c measurements are higher than the ISPAD recommended target [16]. Data describing the patients included in this study are reported in Table 2 and refer to the first HbA1c valid measurement.

Table 1: Number of monitoring windows with different widths: when the window width increases, the number of accepted windows and the number of considered patients decreases.

Windows width	Number of windows accepted	Number of windows discarded	Number of patients	HbA1c, %
30 days	42	35	23	7.35 (6.93–8.48)
60 days	37	40	21	7.30 (6.90–8.50)
90 days	28	49	18	7.25 (6.85–8.10)

Data are presented as frequency, and median (first quartile-third quartile). Windows were excluded if the number of glucose readings was less than 70% of the expected total. Glycated hemoglobin (HbA1c) is expressed in National Glycohemoglobin Standardization Program (NGSP) units.

Table 2: Baseline characteristics of patients.

Variable	Summary statistics
Sex	Female: 12 (52.17%), Male: 11 (47.83%)
Age, years	10.65 (7.92–12.86)
Diabetes duration, years	6.87 (1.67–6.87)

Summary statistics are presented as frequency (percentage), and median (first quartile-third quartile).

Stacked bars in Figure 1 reveal that the average percent partition of time spent below, within, and above range is comparable in windows of 30, 60, and 90 days, with no statistically significant differences (p-value <0.05). It is evident that time spent outside of the 70–180 range (mg/dL) is highly asymmetrical because average TBR (given by the sum of TBR_Lev1 and TBR_Lev2) is less than 3.55% and average TAR (given by the sum of TAR_Lev1 and TAR_Lev2) is greater than 42.42% in all the windows whereas average TIR is between 48.89% (30-days windows) and 54.02% (90-days windows). Average glucose (mg/dL) and percentage CV are 193.28 and 37.64 in 30-day windows, 189.14 and 38.76 in 60-day windows, 179.92 and 38.67 in 90-day

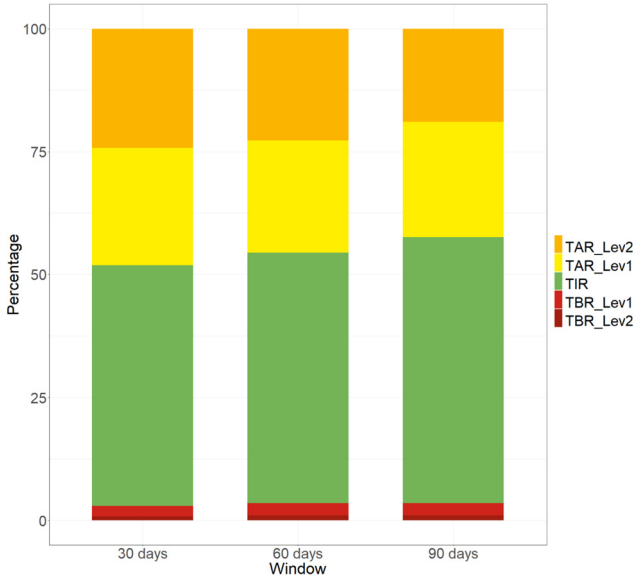

Figure 1: Stacked bar representation of average time in ranges using different window widths. Each stack shows the percentage of time spent within different glucose ranges: Time severely Above Range (TAR_Lev2), Time slightly Above Range (TAR_Lev1), Time in Range (TIR), Time slightly Below Range (TBR_Lev1), Time severely Below Range (TBR_Lev2). To make the interpretation easier, the same colors of the ATTD consensus report [11] are used in the figure.

windows whereas the percentage of windows characterized by a low glycemic variability (CV ≤36% [11]) is equal to 52.38, 43.24 and 46.42, respectively.

CGM metrics, which come across as significant HbA1c predictors (p-value $<10^{-3}$) with all window widths, are presented in Table 3. The variance explained by each linear mixed model is high, with R^2 always above 0.85 except for TAR_Lev2 in 90-days windows (R^2=0.7597). TIR and TIT show a negative linear relationship with HbA1c for each window width (R^2>0.88) whereas TAR, TAR_Lev2, average glucose, and glucose SD show a positive linear relationship with HbA1c (R^2>0.75). TBR is a significant predictor only in the case of windows of 30 and 60 days (R^2=0.8888 and R^2=0.8878, respectively) whereas there is no significant relationship neither between TBR_Lev2 and HbA1c nor between CV and HbA1c with any window widths. The last column (Target) presents the threshold values of each metric required for a safe and effective glycemic control, based on each linear mixed model using the overall estimated intercept. For TIR and TIT, targets represent the minimum percentages of time spent within specific ranges able to maintain HbA1c ≤7% whereas, for the remaining four metrics, targets are the maximum values able to maintain HbA1c ≤7%.

Figure 2 displays the negative relationship between TIR and HbA1c using 30-day windows, with the adoption of the overall estimated intercept for drawing the regression line, according to Eq. (3):

$$\text{HbA1c} = 10.1678 - 0.0482 \cdots \text{TIR}. \quad (3)$$

Instead, estimated random intercepts for each patient are presented in Table 4. Individualized TIR targets represent the minimum percentages of time spent in the range required for a safe glycemic control (HbA1c ≤7%), based on this linear mixed model.

Discussion

Successful usage of CGM technology in routine clinical practice is reported also in pediatric patients with T1D, but unified recommendations for the use of CGM data represent a challenge for pediatric diabetologists.

In the present study, we investigated the relationship between the most common isCGM-derived glycemic metrics and HbA1c in a group of pediatric patients with T1D. All patients wore the isCGM Abbott's FreeStyle Libre sensors and were monitored for an average period of approximately eight months. For a reliable assessment, we analyzed only the glycemic metrics computed in windows where at least 70% of glucose monitoring data were available, as suggested in the ATTD consensus report [11]. On the other hand, we used linear mixed models to properly account for multiple measures of HbA1c, taken about every three months for many patients.

Based on these models, we estimated overall and individualized CGM targets to allow a safe glycemic control, using the 7%-reference for HbA1c and windows of different widths [11,16]. The ATTD consensus recommends that CGM metrics should be considered for clinical care if the monitoring period is at least of 14 days, but a longer CGM period may be required in presence of high glycemic variability [11]. For this reason, we presented the results obtained with windows of 30, 60, and 90 days, then focusing on targets related to 30-day windows, consistently with a recent study on T1D pediatric patients by Piona et al. [21], which reports that a four-week period is the optimal sampling window for reflecting a long-term glycemic control with CGM data.

Compared to other researches, our study focused on glucose monitoring data of only pediatric patients using isCGM sensors, with the innovative adoption of linear mixed models for exploring the inter-subject variability

Table 3: Separate linear mixed model predictor variables (p-value $<10^{-3}$) with different window widths. Predictor coefficients are presented as value (lower 95% confidence limit; upper 95% confidence limit) whereas intercept coefficients are presented as fixed effect value ± random effect within-patient standard deviation.

Windows width	Predictor		Intercept	R^2	Target
	Variable	Coefficient			
30 days	TIR (%)	−0.0482 (−0.0598; −0.0366)	10.1678 ± 0.5413	0.8965	65.72 (%)
	TIT (%)	−0.0500 (−0.0653; −0.0348)	9.4176 ± 0.6927	0.8871	48.27 (%)
	TAR (%)	+0.0449 (+0.0340; +0.0558)	5.6673 ± 0.5572	0.8984	29.68 (%)
	TAR_Lev2 (%)	+0.0522 (+0.0414; +0.0631)	6.5325 ± 0.4171	0.8729	8.95 (%)
	Average glucose (mg/dL)	+0.0213 (+0.0170; +0.0256)	3.7036 ± 0.4274	0.8860	155 (mg/dL)
	Glucose SD (mg/dL)	+0.0422 (+0.0275; +0.0569)	4.7831 ± 0.7061	0.8701	53 (mg/dL)
60 days	TIR (%)	−0.0591 (−0.0708; −0.0475)	10.6973 ± 0.4726	0.9492	62.52 (%)
	TIT (%)	−0.0650 (−0.0801; −0.0499)	9.8788 ± 0.5828	0.9428	44.30 (%)
	TAR (%)	+0.0549 (+0.0439; +0.0659)	5.2025 ± 0.4921	0.9503	32.76 (%)
	TAR_Lev2 (%)	+0.0561 (+0.0443; +0.0679)	6.4403 ± 0.4097	0.8916	9.98 (%)
	Average glucose (mg/dL)	+0.0234 (+0.0192; +0.0276)	3.3012 ± 0.3778	0.9238	158 (mg/dL)
	Glucose SD (mg/dL)	+0.0429 (+0.0279; +0.0580)	4.6149 ± 0.7353	0.9051	56 (mg/dL)
90 days	TIR (%)	−0.0598 (−0.0734; −0.0463)	10.7226 ± 0.3894	0.9191	62.24 (%)
	TIT (%)	−0.0641 (−0.0811; −0.0471)	9.7751 ± 0.4961	0.9128	43.29 (%)
	TAR (%)	+0.0544 (+0.0418; +0.0671)	5.2163 ± 0.3608	0.8933	32.78 (%)
	TAR_Lev2 (%)	+0.0650 (+0.0491; +0.0809)	6.2934 ± 0.7015	0.7597	10.87 (%)
	Average glucose (mg/dL)	+0.0272 (+0.0218; +0.0325)	2.6410 ± 0.3328	0.8279	160 (mg/dL)
	Glucose SD (mg/dL)	+0.0457 (+0.0280; +0.0634)	4.3573 ± 0.6176	0.8530	58 (mg/dL)

TIR, Time in Range; TIT, Time in Target Range; TAR, Time Above Range; TAR_Lev2, Time severely Above Range; SD, Standard Deviation.

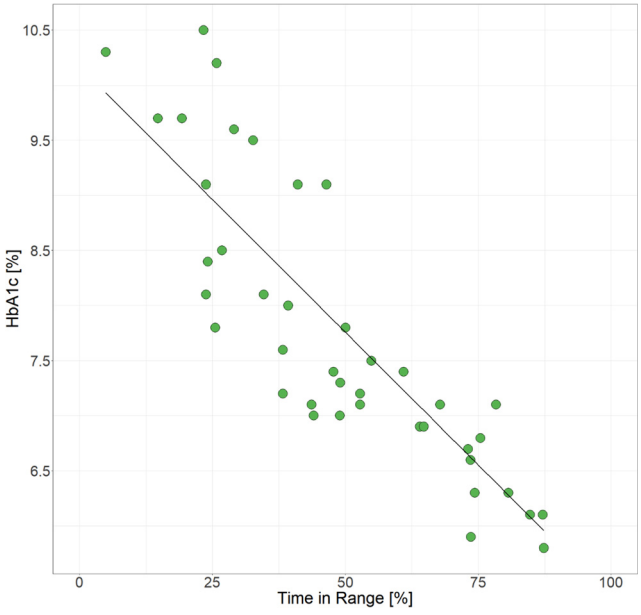

Figure 2: Example of a linear relationship (p-value $<10^{-7}$) between glycated hemoglobin (HbA1c) and Time in Range (70–180 mg/dL) using 30-days windows. HbA1c is expressed in National Glycohemoglobin Standardization Program (NGSP) units.

and identifying also individualized CGM targets. According to the ATTD consensus report, in fact, individualized targets are important especially for children, adolescents, and young adults [11].

Overall, the results obtained are very close to the ones reported in the consensus recommendations for safe glycemic control. Indeed, the targets found in our study with linear mixed models using the overall estimated intercepts (Table 3) are comparable with the guidance on targets provided by the ATTD consensus report [11], that recommends a TIR >70%, TAR <25%, and TAR_Lev2 <10%. Results presented in Table 3 are consistent even with other findings reported in the literature [12, 23, 24, 9]. Beck et al. [10] analyzed through linear regression models the relationship between HbA1c and CGM glycemic metrics in T1D adult patients, across four randomized trials. Based on data at the beginning of the study, targets for a safe glycemic control were set at 70% for TIR, at 46.73% for TIT, and at 24.89% for TAR, but based on data at the end of the study these targets were set at 64.63, 42.56, and 30%, respectively. Vigersky and McMahon [22] selected paired HbA1c and TIR values from 18 studies, considering patients with type 1 or type 2 diabetes, and they concluded that the TIR target should be set around 65%. Petersson et al. [23] focused on translating HbA1c into time spent in the glucose target range in a T1D pediatric population using both rtCGM and isCGM systems. The authors adopted a nonlinear regression model on 60-day windows, setting the TIT target at 50% for maintaining HbA1c ≤6.5%, therefore it can be considered around 41% for HbA1c ≤7%, similar to our study target of 44.30% in 60-day windows.

Table 4: Example of estimated random intercepts and Time in Range (TIR) target values for maintaining glycated hemoglobin (HbA1c) ≤7% using 30-days windows.

Patient	Average HbA1c, %	Average TIR	Intercept	TIR target, %
4	7.25	42.70	9.4129	50.06
7	7.40	41.41	9.5164	52.20
15	8.10	23.77	9.5749	53.42
19	7.10	48.40	9.5926	53.79
2	7.30	49.03	9.8435	58.99
1	7.00	58.38	9.8911	59.98
8	8.50	26.77	9.9252	60.69
5	8.00	39.24	9.9902	62.03
6	6.35	74.51	9.9909	62.05
3	7.20	59.81	10.1016	64.35
26	6.23	80.72	10.1309	64.95
23	8.68	30.48	10.1409	65.16
24	6.10	84.76	10.1793	65.96
11	7.80	50.00	10.1950	66.28
21	9.40	19.24	10.2927	68.31
20	7.10	67.83	10.2976	68.41
22	6.72	74.64	10.3030	68.52
17	10.30	4.94	10.4060	70.66
9	9.70	19.27	10.4644	71.87
27	9.60	29.06	10.7034	76.83
14	9.10	41.01	10.7522	77.84
16	9.10	46.42	10.9199	81.32
10	10.35	24.51	11.2353	87.86

HbA1c is expressed in National Glycohemoglobin Standardization Program (NGSP) units.

To complete the comparison, we have explored also quadratic mixed models. TIT was the only CGM metric that showed a curvilinear relationship with HbA1c in 60-day windows (R^2=0.9463), and quadratic Time in Target Range term (TIT^2) turned out to be a significant predictor variable (p-value = 0.0463). Additionally, considering the linear mixed model with average glucose as a predictor, the overall coefficients are almost the same as in the linear regression equation used to convert the CGM-derived average glucose to an agreed-upon glucose indicator called Glucose Management Indicator (GMI), where intercept and predictor coefficients are 3.31 and 0.02392 [24].

However, our approach allows investigating also the question of individualized CGM targets to meet the needs of each T1D subject, as advised in the ATTD consensus report [11]. This direction is suggested also by the Juvenile Diabetes Research Foundation CGM Study Group [25], which found that a substantial individual variability exists in the relationship between average glucose and HbA1c, and by Bergenstal et al. [24], who pointed out that people with the same average glucose or calculated GMI could have different HbA1c value. We have verified that age or sex showed no clear relationship with HbA1c whereas it can be assumed that the different intercept values of the regression lines are related to the individual biological variation in erythrocyte survival or glycation rates, as hypothesized for GMI by both the Juvenile Diabetes Research Foundation CGM Study Group [25] and Bergenstal et al. [24]. In case this variability is attributed to biological or genetic factors, further studies on longer monitoring periods may confirm that the relationship between CGM metrics and HbA1c in the same patient remains stable over time.

Table 4 shows that the random effect represented by the patient's specific intercept has a high variability (ranging in the interval 9.4129–11.2353), which is reflected in the wide range of TIR targets estimated by the model (ranging in the interval 50.06–87.86). These outcomes suggest that some patients could maintain a lower TIR to preserve HbA1c ≤7%, whereas other patients need to stay in the range for a longer period to keep HbA1c within the same target. This result may be influenced by the difference between long-term average glucose from HbA1c and short-term average glucose during CGM [26], emphasizing the importance of individualized diabetes management also using the CGM metrics, particularly in patients with sub-optimally controlled diabetes.

We acknowledge several limitations of our study. The number of investigated patients is limited, and nobody showed early complications such as retinopathy, nephropathy, or established macrovascular disease. In addition, isCGM may be less accurate than direct glucose measurements, even if the FreeStyle Libre accuracy has been verified specifically for the pediatric population [15]. Although further studies are needed to strengthen our observation, this result is valuable to improve the glycemic control of patients.

In conclusion, in the present study, we confirm the relationship between several CGM metrics and HbA1c. Additionally, we report that a different TIR would be required to achieve the same HbA1c target in different patients, pointing out the importance of an individualized interpretation of the CGM data.

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Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Fondazione IRCCS Policlinico San Matteo Hospital in Pavia, Italy (code number 20180056724). Childs' caregivers (or subjects aged ≥18 years) gave written informed consent for inclusion in the study.

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