Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: December 31, 2023

Citation: Al-Taie, B., et al., 2023. Continuous Glucose Monitoring Variables and HbA1c in Children and Adolescents with Type 1 Diabetes. Medical Research Archives, [online] 11(12). https://doi.org/10.18103/mra.v11i12.4858

DOI: https://doi.org/10.18103/mra.v11i12.4858

ISSN: 2375-1924

RESEARCH ARTICLE

Continuous Glucose Monitoring Variables and HbA_{1c} in Children and Adolescents with Type 1 Diabetes

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ABSTRACT

Objective: Associations between Continious Glucose Monitoring (CGM) variables (metrics) and HbA_{1c} is not well understood. In this exploratory study we assessed the association between mean sensor glucose (mean CGM) and HbA_{1c} and how it is affected by sensor type (real-time CGM vs. intermittent scanned CGM), patient characteristics, and other CGM variables in children and adolescents with type 1 diabetes.

Methods: Data were obtained from Swedish paediatric diabetes quality registry (SWEDIABKID) and Diasend. Paired HbA_{1c} and CGM data collected within one year were analyzed, including a maximum of four individual HbA_{1c} at least 2 months apart and for which CGM data were available for 12 weeks prior to HbA_{1c}.

Results: 174 children were included of whom 141 had a diabetes duration ≥ 1-year; 71 used real-time CGM and 70 used intermittent scanned CGM. The intermittent scanned CGM children were older, had a higher proportion of children on insulin injections versus pump, and more CGM recordings during an 8-week registration. A stronger correlation between HbA_{1c} and mean CGM was observed based on a sensor period ≥ 8 weeks preceding HbA_{1c} in children with ≥ 1-year diabetes duration (r= 0.70, $p<0.01$). HbA_{1c} was more weakly correlated with Time In Range (r=-0.40, $p<0.01$). Low HbA_{1c} and low CGM Standard Deviation and, for intermittent scanned CGM, higher daily sensor duration was associated with a stronger correlation between mean CGM and HbA_{1c}. HbA_{1c} was dependent on Time Above Range and Time Below Range in intermittent scanned CGM users while in real-time CGM only Time Above Range impacted.

Conclusions: HbA_{1c} correlated only moderately with mean CGM and discrepancies should be expected for the child with short diabetes duration, high HbA_{1c} or high CGM Standard Deviation.

Keywords: Continuous glucose monitoring; Time in range (TIR), Children; Diabetes type 1; HbA1c.

Introduction

The use of Continuous Glucose Monitoring devices (CGM) in the management of type 1 diabetes mellitus is rapidly increasing particularly in children. In Sweden, 3.8 % of children (0-17 years of age) with type 1 diabetes used CGM in 2015 and the mean HbA_{1c} was 58 mmol/mol (7.5 %). The use of CGM is rapidly approaching 100% and the most recent mean HbA_{1c} was 51.6 mmol/mol (6.9 %) in the 2022 SweDiabkids report[1]. The main goal of diabetes glycemic control is still defined by HbA1c, due to the large body of evidence of its association with long term complications. "Today, CGM technology is at the heart of diabetes management" and "CGM specific metrics, in particular "Time In Range (TIR)" (defined as percentage of time with sensor readings between 70 and 180 mg/dl, 3.9 and 10 mmol/L) have been adopted as useful clinical markers"; quotes from ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Glucose monitoring[2]. However, the evidence establishing the association of HbA_{1c} with CGM variables are very limited. Moreover, data claimed to support that TIR is the more important CGM variable is based on once every 3 months, 7 points capillary glucose measurements (self-monitoring of blood glucose) and its association with HbA_{1c} and is not based on CGM measurements[3,4]. Furthermore, the evidence is entirely based on data from adults.

The CGM technology include the sensor device real-time Continuous glucose monitoring (rtCGM)[5-8] and the intermittent scanned CGM (isCGM) which needs scanning by the patient[8,9]. Both rtCGM and isCGM reports real-time interstitial glucose values as well as the direction, magnitude, and duration of fluctuations in blood glucose based on the most recent readings. Unlike a single value of HbA_{1c}, which is of limited help in the daily adjustment of insulin dosing, or the self-monitoring of blood glucose (SMBG), which requires frequent (and painfull) testings every day, along with its sporadic nature, sensor data enables display of trend graphs while also registering data during sleep allowing a retrospective analysis of patterns of hyperglycemic spikes and asymptomatic hypoglycemia that may otherwise be missed[6-11].

Recent Swedish recommendations that defines a good glycemic control in children with type 1 diabetes as a HbA_{1c} level < 48 mmol/mol (6.5 %) without severe hypoglycemia may, in the majority of children, be obtainable only with help from CGM[12]. The use of CGM offers direct real-time feedback to the user and rtCGM has been demonstrated in meta-analyses comparing it to self-montoring of blood glucose (SMBG) to achieved lower HbA_{1c} levels in children and adults with type 1 or 2 diabetes[5,13,14]. In a recent prospective study of adults with type 1 diabetes, isCGM use lowered HbA_{1c} over one year where also more hypoglycemia was reported[15]. The frequency of severe hypoglycemia was reduced in adults using rtCGM[16]. Also, a controlled crossover trial comparing rtCGM to SMBG in pediatric type 1 diabetes showed significantly decreased HbA_{1c} levels[17]. The frequency of sensor use is a major predictor of this effect[5,9,14,18].

HbA_{1c} is the measure of glycemic control that consistently has been shown to predict the risk of later development of long-term diabetic vascular complications such as in the

Diabetes Control and Complications Trial (DCCT) and more recent studies with long-term follow-up[19-21]. HbA_{1c} is thought to closely reflect blood glucose levels over the preceding weeks to 2-3 months. The imperfect correlation between 4-8 point SMBG and HbA_{1c} has been suggested to mainly depend on few measurements during the day and even less observations during the night. This assumption has been addressed by more recent studies where HbA_{1c} has been correlated with mean glucose estimates derived from individual rtCGM data[9-11]. As pointed out by Beck et al[10], rtCGM data with higher coverage of the diurnal glucose fluctuations did not markedly improve the correlation, suggesting that other factors are of importance. In the current explorative study we have assessed which factors related to diurnal glucose fluctuations measured by modern CGM may explain this lack of individual consistency between HbA_{1c} and the mean sensor glucose (mean CGM) including glucose variability (reported as CGM standard deviation; CGM SD), TIR, in hypoglycemia (reported as Time Below Range; TBR), or in hyperglycemia (reported as Time Above Range; TAR), all factors that may affect HbA_{1c}[5,9-11,22,23]. Other factors that may impact on the association between HbA_{1c} and mean CGM including diabetes duration, rapid improvements in glycemia and insulin pump versus injection usage were studied. Finally, we assessed whether the use of isCGM versus rtCGM differed in their correlation to HbA_{1c}, which to our knowledge has not previously been reported, and is considered necessary to provide evidence of CGM value for all patient groups (24). In daily practice, these are essential questions since the patient and the diabetes team are not seldom confronted with large discrepancies between corresponding HbA_{1c} and CGM data.

Subjects and methods

DATA EXTRACTION AND PARTICIPANTS

This is a retrospective, registry-based, explorative study of children and adolescents with type 1 diabetes born 1999-2014. They were actively followed at H.R.H Crown Princess Victoria's Childrens' and Youth Hospital in Linköping during the period 1st December 2016 – 31st January 2018 with available CGM sensor data in Diasend; 2, 4, 8, and 12 weeks preceeding at least one HbA1c determination. Patients were registrered in the Swedish national quality registry for diabetes in children and adolescents (Swediabkids) and patients characteristics were downloaded from the registrer and/or from patient's E-journal. A maximum of four HbA1c at least 2 months apart and corresponding CGM sensor data summarized by the Diasend software were collected.

The study was conducted after an ethical approval from the Regional Ethics Committee in Linköping, Sweden.

Additional patient variables included age, gender, Body Mass Index (BMI) SDS, duration of diabetes, and method of insulin delivery being Multiple daily insulin injections (MDI) or Continuous subcutaneous insulin infusion/ insulin pump (CSII). The patients used either rtCGM or isCGM sensor devices inserted subcutaneously for glucose control and prescribed in accordance with the Swedish Guidelines of CGM for Children and Adolescents with type 1 diabetes[12]. The rtCGM monitors real-time interstitial glucose

concentration every 10 seconds and logs a value every 5 minutes. The isCGM monitors real-time interstitial glucose concentration every minute and logs a value every 15 minutes, however, there is a need for the patient to swipe a separate touch screen reader device near the sensor for transmitting real-time tissue glucose levels of the preceeding 8-hours[8,9,11].

CGM data from the summary page in Diasend were downloaded for specific time-periods preceeding the available HbA_{1c} values. We did not download 5 minutes raw-data for external data-analysis. The CGM read-outs include: Mean (mean CGM), Median (median CGM), AUC high, AUC low, Highest value, Lowest value, Standard deviation (CGM SD), Values per day, Values per selected period), Values above target, Values within target, Values below target, Average daily sensor duration, and Total sensor duration. Values within, below or above target reflects the number of registered values spent within, below, or above a patient's target glucose range and given as a percentage of the total number of values it is equal to time in range (TIR), time below range (TBR) and time above range (TAR). The recommendation at the time of data collection was to use threshold values of < 4 mmol/L for hypoglycemia and > 10 mmol/L for hyperglycemia to accommodate recommended post-prandial levels at the time. With a few exceptions, individual settings were aligned with recommendations and is in agreement with the current thresholds recommended by ISPAD[2].

The Swediabkids registry[1] includes > 90% of all children with type 1 diabetes in Sweden. During the calendar year 2017, data on 7594 patients were available in Swediabkids and 6571 or 90,6 (95 % confidence interval; 89,9 - 91,3) % of all children used CGM/FGM. According to the registry, 92,6 (89,1 - 96,1) % of the children in our clinic used a sensor. All registry children using rtCGM/isCGM had a mean age of 12.3 years and their mean (95 % confidence interval) HbA1c was 56,8 (56,5 - 57,1) mmol/mol or 7.3 (7.26 – 7.33) %. Data are available online at https://www.ndr.nu/#/knappen.

SUBGROUPS

Subgroup analysis was performed on children with diabetes duration <1 year or ≥ 1 year (as a rough separation of patients with significant endogenous insulin production or less) and on children with rtCGM or isCGM sensors. The most commonly used sensors were Dexcom G4 or G5 (rtCGM) and FreeStyle Libre Flash (isCGM).

The average daily sensor duration (given in %) was based on the number of logged values relative to the maximal possible number. When assessing the profile summary in Diasend some patients (using isCGM) had number of values exceeding the maximal possible number since every scan added a logged reading. Therefore, we re-assessed the total isCGM sensor duration by manually counting the number of these extra scans to make appropriate corrections. In randomly selected patients with isCGM (n=20), there was a maximum of 10%-units discrepancy between readouts and manually counted readings. Therefore, the readout data have been used.

We compared the impact of the 8-week sensor duration on the correlation between HbA_{1c} and 8-week mean sensor glucose levels (mean CGM) in rtCGM and isCGM subgroups separately. Also, we analyzed the impact of

glucose fluctuations, extracted as a value of Standard Deviation from the sensor data, on the correlation between HbA_{1c} and 8-week mean CGM demonstrated in three different ranges of HbA_{1c} (< 50, 50-60, and ≥ 60 mmol/mol or < 6.7, 6.7-7.6, and > 7.6 %). The dependecy of gender (male/female) and insulin therapy (MDI/CSII) used during the 8-week period on HbA_{1c} was demonstrated in the total CGM population, Finally, we tracked and presented data of twelve children with four complete sets of HbA_{1c}–8w mean CGM over one year to investigate any pattern of glycation-differences among individual patient.

STATISTICAL ANALYSES

All demographics are presented as mean ± SD if normally distributed and median (IQR) if not. Independent Samples T-test and Mann-Whitney U-Test were used when appropriate. Spearman correlations were performed in subgroups. Variables found by bivariate analysis to be associated with HbA_{1c} were inserted in a multiple regression analysis performed on the dependent variable HbA_{1c}. The statistical program SPSS version 24 was used. The level of significane was set as $p < 0.05$.

Results

THE STUDY POPULATION

We identified 210 children with type 1 diabetes registered in the SweDiabKids database and treated in our center. Of these, 36 patients were not included either due to lack of sensor data or lack of account on the online-platform Diasend. In total, CGM data was available on 174 children (83%), of which 141 children had a duration of diabetes equal to or greater than one year, and of those 71 used rtCGM and 70 used isCGM (Fig. 1). As shown in Table 1, the isCGM children were older than the rtCGM patients, had a higher proportion of children with MDI treatment, and more CGM recordings (sensor duration) during the 8-week sensor period.

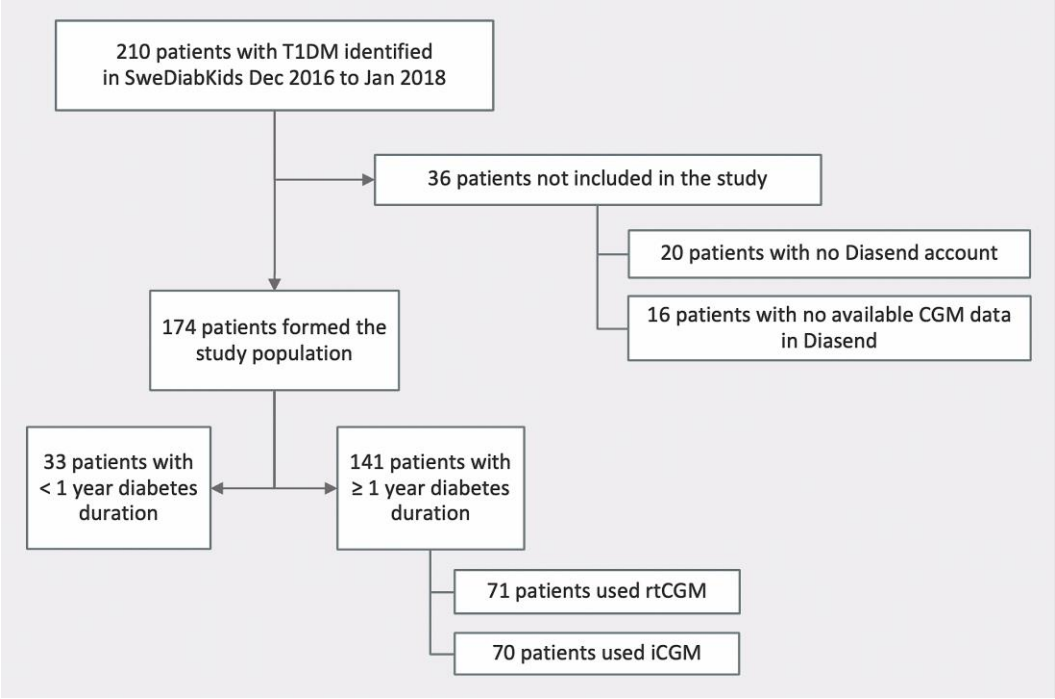

Fig . 1 Flowchart on patient inclusion.

Table 1 Patient characteristics of the study population and subgroups.

	All	≥ 1-year diabetes duration		
Parameters	rtCGM + isCGM	rtCGM + isCGM	rtCGM	isCGM
n	174	141	71	70
Age (years)	11.7 (±4.1)	12.0 (±3.9)	10.0 (±3.8)	14.0 (±2.9) *
Gender (% female)	47	47	44	46
BMI SDS	0.8 (6.4)	0.69 (1.8)	0.56 (1.8)	1.0 (1.9)
Diabetes duration (yrs)	3.5 (6.0)	4.8 (5.4)	4.5 (4.9)	5.6 (5.8)
Insulin therapy MDI or SCII (% MDI)	50	44	20	69 *
HbA_{1c} (mmol/mol)	56.1 (±10.9)	54.8 (±8.9)	55.4 (±7.5)	54.2 (±10.2)
HbA_{1c} (%)	7.1 (±1.4)	7.2 (±1.2)	7.2 (±1.0)	7.1 ((±1.3)

Data are mean (±D) or median (IQR); ND= Not determined; * P= < 0.0001 versus rtCGM subgroup

CORRELATION BETWEEN HBA_{1C} AND MEAN CGM – IMPACT OF DIABETES DURATION, TYPE OF SENSOR DEVICE AND SENSOR PERIOD

The correlation between HbA_{1c} and mean CGM values was weak in the 174 patients independent of the sensor period (Table 2). In patients with diabetes duration < 1 yr there was no correlation (Fig. 2). In patients with diabetes duration ≥ 1 yr a significant correlation was found for the 8-weeks duration recordings ($r = 0.70$, $p< 0.01$) and no further improvement was seen for 12-weeks data. The rtCGM and isCGM performed similarly in predicting HbA_{1c} in patients with longer diabetes duration (≥ 1 yr) and better with 8- and 12- week sensor periods. Despite of the significant correlation, the individual with an average HbA_{1c} of about 55 mmol/mol (7.2 %) may have a mean CGM ranging from about 7 to 12 mmol/L.

Table 2 Correlations performed on HbA_{1c} vs. mean CGM at the preceding 2, 4, 8, and 12 weeks presented in subgroups divided based on sensor device and diabetes duration.

	All	≥ 1-year diabetes duration		
Sensor period	rtCGM+isCGM	rtCGM+isCGM	rtCGM	isCGM
n	174	141	71	70
2w mean CGM (mmol/L)	0.36	0.61	0.58	0.64
4w mean CGM (mmol/L)	0.39	0.64	0.61	0.70
8w mean CGM (mmol/L)	0.42	0.70	0.69	0.72
12w mean CGM (mmol/L)	0.41	0.68	0.70	0.71

Data are r-values from Spearman correlations. All correlations are significant at p< 0.01

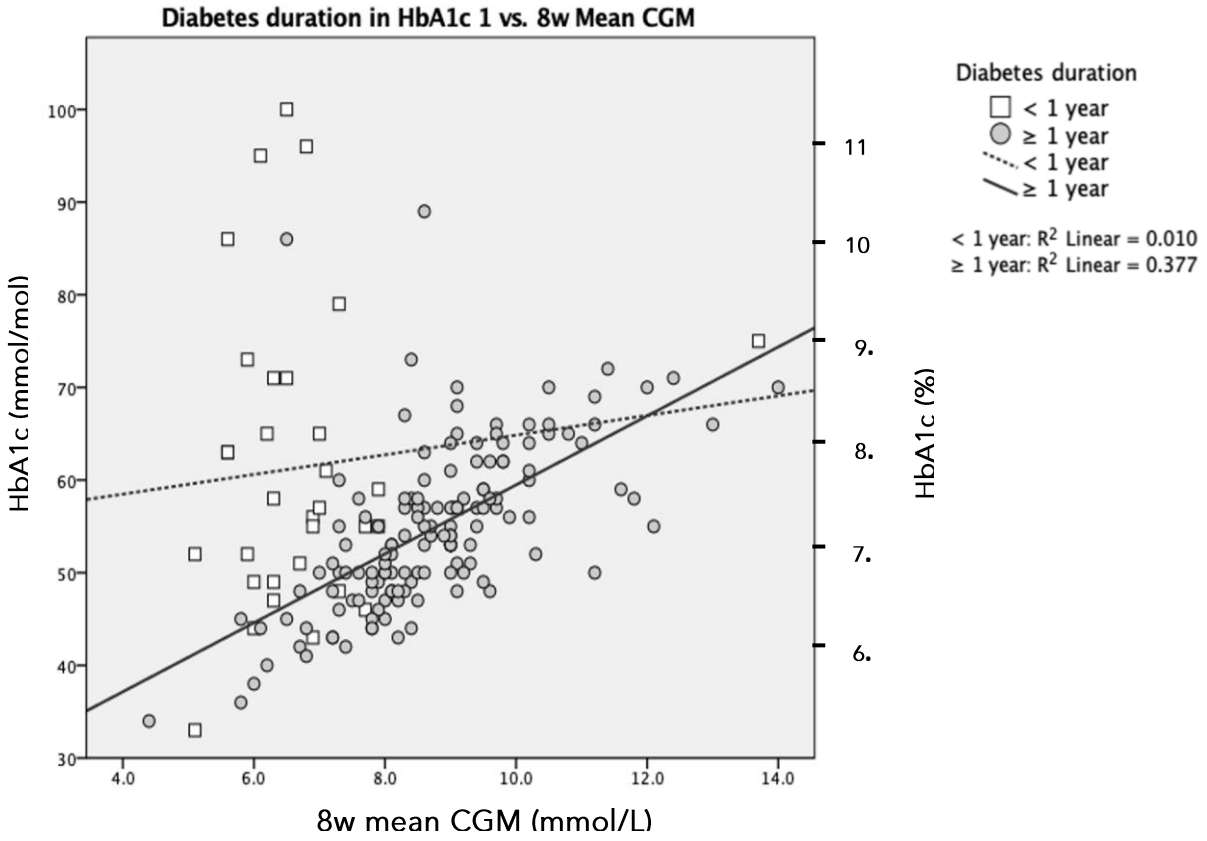

Fig. 2 The relationship between HbA_{1c} (mmol/mol) and mean CGM (mean sensor glucose; mmol/L) at the preceding 8 weeks in rtCGM+isCGM in the two subgroups of diabetes duration; ≥ 1-year and < 1-year. White squares: < 1 year, dark circles: ≥ 1 year, straight line: < 1 year, and dotted line: ≥ 1 year of diabetes duration.

HBA_{1C} AND 8-WEEK CGM VARIABLES IN PATIENTS WITH DIABETES DURATION > 1 YEAR

Correlation among HbA_{1c} and CGM variables

On a group basis the rtCGM and isCGM children had similar mean CGM (Table 3) in accordance with their similar HbA_{1c}. The CGM SD correlated with HbA_{1c} for both rtCGM and isCGM children, a finding that is likely to be confounded by a strong correlation between mean CGM and CGM SD.

In rtCGM children, HbA_{1c} correlates positively to the AUC high (r = 0.718, p <0.01) while there is no correlation to AUC low. In contrast, isCGM children demonstrated a positive correlation of HbA_{1c} to AUC high (r = 0.581, p <0.01) as well as a negative correlation of HbA_{1c} to AUC low (r = -0.287, p <0.05). The isCGM children also spend more time in hypoglycemia as indicated by double the mean AUC low and double the mean TBR compared to the rtCGM children. Similar data were found for TAR and TBR. Furthermore, there was a negative correlation between HbA_{1c} and TIR in both groups, although with a lower correlation coefficient (r) compared to that between HbA_{1c} and mean rtCGM and mean isCGM, respectively.

At the high median (IQR) sensor duration in children with isCGM (91 (108) %) the variation does not explain the level of HbA_{1c}. Even in children with rtCGM, who had a significant lower sensor duration (53 (71) %), the variation did not explain the level of HbA_{1c}.

Table 3 CGM parameters in rtCGM and isCGM groups and spearman correlations versus HbA_{1c}. Sensor data represents the preceding 8 weeks from obtaining HbA_{1c} in patients with ≥ 1-year diabetes duration. Mean (SD) and median (IQR) are presented for each CGM parameter.

	rtCGM (n= 71)			isCGM (n=70)		
CGM parameters	Mean (SD)	Median (IQR)	R vs HbA_{1c}	Mean (SD)	Median (IQR)	R vs HbA_{1c}
8w mean CGM (mmol/L)	*8.6 (1.2)*	*8.5 (7.5)*	*0.691***	*8.7 (1.6)*	*8.7 (8.0)*	*0.724***
8w median CGM (mmol/L)	8.1 (1.3)	8.0 (8.5)	0.659**	8.1 (1.8)	7.8 (9.0)	0.726**
8w CGM SD (mmol/L)	3.6 (0.8)	3.4 (3.9)	0.666**	4.22 (1.08)	4.4 (4.5)	0.511**
8w AUC high (>8-10 mmol/L)	1.14 (0.80)	1.00 (4.8)	0.718**	1.50 (1.03)	1.35 (4.60)	0.581**
8w AUC low (<4 mmol/L)	0.048 (0.053)	0.000 (0.2)	0.082	0.129 (0.124)	0.100 (0.8)	-0.287*
8w values above target [TAR] n [%]	3557 (1932) [33.8 (13.1)]	3195 (8269) [34.1 (17.1)]	0.523**	1606 (911) [35.6 (16.3)]	3195 (8269) [35.8 (22.3)]	0.408**
8w values within target [TIR] n [%]	6115 (2481) [58.6 (12.6)]	5701 (10422) [57.7 (18.3)]	-0.392**	1606 (911) [50.2 (15.1)]	3195 (8269) [49.1 (18.2)]	-0.408**
8w values below target [TBR] n [%]	733 (444) [7.48 (4.42)]	662 (2150) [6.90 (5.16)]	-0.058	1606 (911) [14.1 (8.83)]	3195 (8269) [12.8 (8.7)]	-0.493**
8w sensor duration (%)	64 (20)	53(71)	-0.036	81 (24)	91 (108)***	-0.155

Data are r-values from Spearman correlations.

*Correlation is significant at p< 0.05

**Correlation is significant at p< 0.01

*** p<0.001 vs. rtCGM group

Impact of sensor duration and glucose variability (CGM SD) on the correlation between HbA$_{1c}$ and mean CGM

In rtCGM children there was no major impact of daily sensor duration (below or above median) on the correlation between HbA$_{1c}$ and mean CGM (r= 0.701 and r= 0.665, respectively, both p <0.01) (Fig. 3.a,b). In isCGM children the correlation appeared to be stronger in patients with a sensor duration above the median (r= 0.898 vs. r= 0.586, both p <0.01) (Fig. 4a,b).

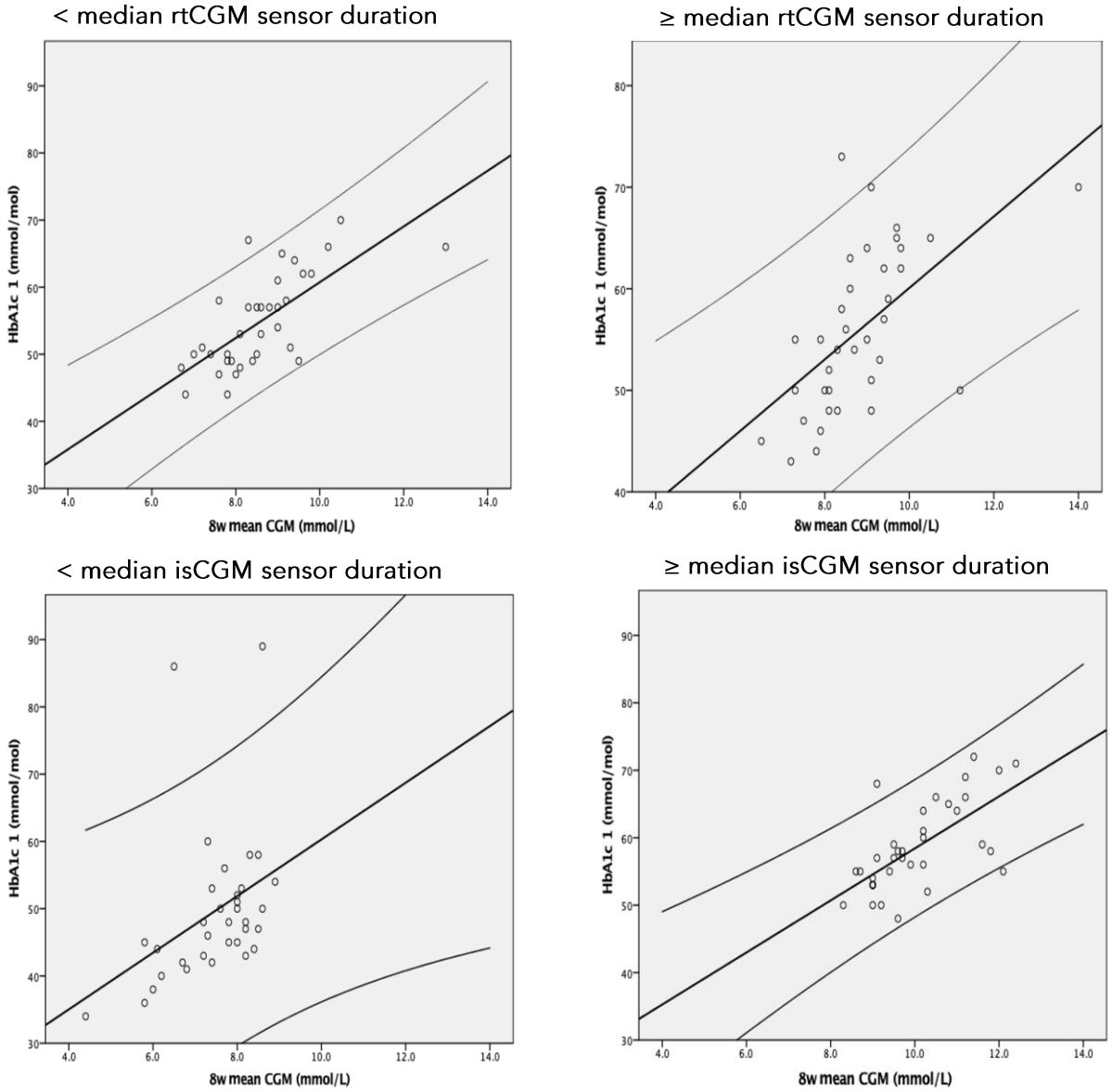

Fig. 3a, 3b (Top) Sensor duration in rtCGM patients presenting the correlation between HbA$_{1c}$ (mmol/mol) and 8-week mean CGM (mean sensor glucose; mmol/L) in the two subgroups less than the median of sensor duration (n= 35, r= 0.701, p<0.01) and greater than or equal to the median of sensor duration (n= 36, r= 0.665, p<0.01). The best-fit line is shown for all graphs. The two curved lines represent the 95% confidence interval for the data points.

Fig. 4a, 4b (Bottom) Sensor duration in is CGM patients presenting the correlation between HbA$_{1c}$ (mmol/mol) and 8-week mean CGM (mean sensor glucose; mmol/L) in the two subgroups less than the median of sensor duration (n= 34, r= 0.586, p<0.01) and greater than or equal to the median of sensor duration (n= 36, r= 0.898, p<0.01).

We also assessed the correlation between HbA_{1c} and mean CGM and how it is affected by three different ranges of HbA_{1c} (< 50, 50-60, ≥ 60 mmol/mol or < 6.7, 6.7-7.6, and > 7.6 %) and whether CGM SD was below (Fig. 5a,b,c) or above the median (Fig. 6a,b,c). In this analysis we combined rtCGM and isCGM data. Most children with excellent metabolic control (HbA_{1c} < 50 mmol/mol or < 6.7 %) had a low CGM SD and the correlation was significant (r = 0.60, p= 0.01) (Fig. 5a). Very few patients had a CGM SD above the median and a low HbA_{1c} or a CGM SD below the median and a higher end HbA_{1c} (Fig. 5c and 6a) and the correlations cannot be evaluated. Several patients in the midrange HbA_{1c} fell into either below or above median CGM SD with very poor and insignificant correlations in both groups (p-values not reported) (Fig. 5b and 6b). As expected, at a higher HbA_{1c} there was several patients with high CGM SD but the mean CGM did not have any predictive value of the HbA_{1c} and the correlation was poor and insignificant (p-value not reported) (Fig. 6c).

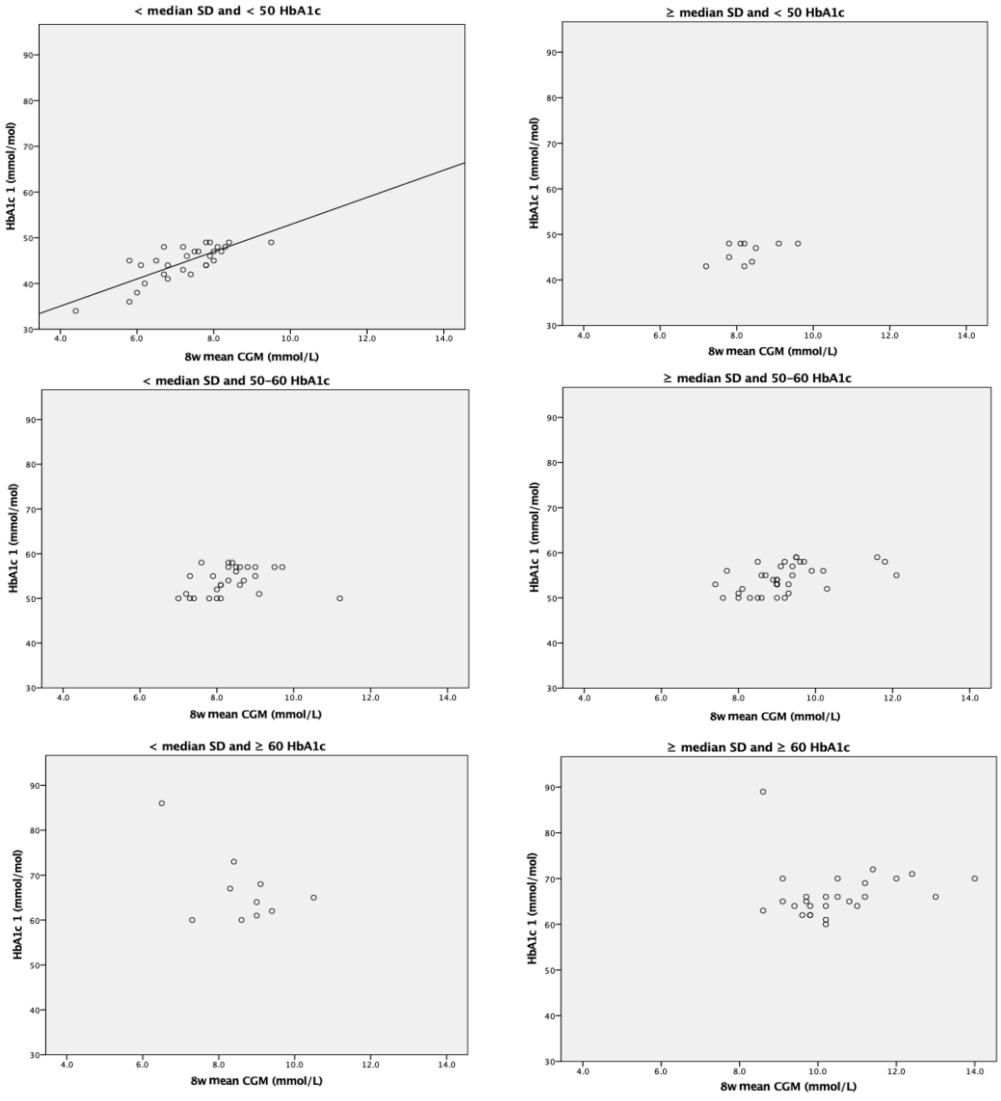

Fig. 5a, 5b, 5c (Left) The relationship between HbA_{1c} (mmol/mol) and 8-week mean CGM (mean sensor glucose; mmol/L) in three different HbA_{1c} ranges when the CGM SD is less than the median value.

Fig. 6a, 6b, 6c (Right) The relationship between HbA_{1c} (mmol/mol) and 8-week mean CGM (mean sensor glucose; mmol/L) in three different HbA_{1c} ranges when the CGM SD is equal to or above the median value.

Multiple regression analysis of HbA_{1c} dependence on CGM variables and patient characteristics

Multiple regression analysis demonstrated a statistically significant dependency of HbA_{1c} on mean CGM glucose [Standardized coefficients (ß), 0.54; $p < 0.001$] (Table 4). However, variables such as CGM SD, insulin therapy and diabetes duration did not significantly contribute as predictors of HbA_{1c} (all with $p > 0.05$). The Adjusted *r* squared (Adj. r^2) for the multiple regression model was 0.376.

Table 4 Multiple regression model to assess the influence of some CGM variables (found by bivariate analysis to be associated with HbA_{1c}) and patient characteristics on HbA_{1c}.

	Coefficients†			t	Sig.
	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta		
(Constant)	21.640	3.633		5.956	0.000
8w mean CGM (mmol/L)	3.282	0.569	0.541	5.768	0.000
8w CGM SD	1.031	0.893	0.114	1.154	0.251
Insulin therapy (0=injection, 1=pump)	2.151	1.223	0.120	1.759	0.081
Diabetes duration (years)	-0.137	0.190	-0.052	-0.722	0.472

†Dependent Variable: HbA_{1c}

Tracking of HbA_{1c} vs. mean CGM glucose over time – an indicator of individual glycation ability?

Data of twelve children with four consecutive 3-months periods of CGM data in a one-year period was assessed to track changes in HbA_{1c} and mean CGM relationship (Fig. 7). If the ability to glycate HbA_{1c} was largely different among individuals, one individual would be expected to track markedly below or above the overall correlation line (not shown). However, this was not found. Rather it appeared that there was a regression to the mean effect, suggesting that the position of HbA_{1c} and mean CGM pairs, that were outliers from the correlation line, was rather due to changes in metabolic control over time.

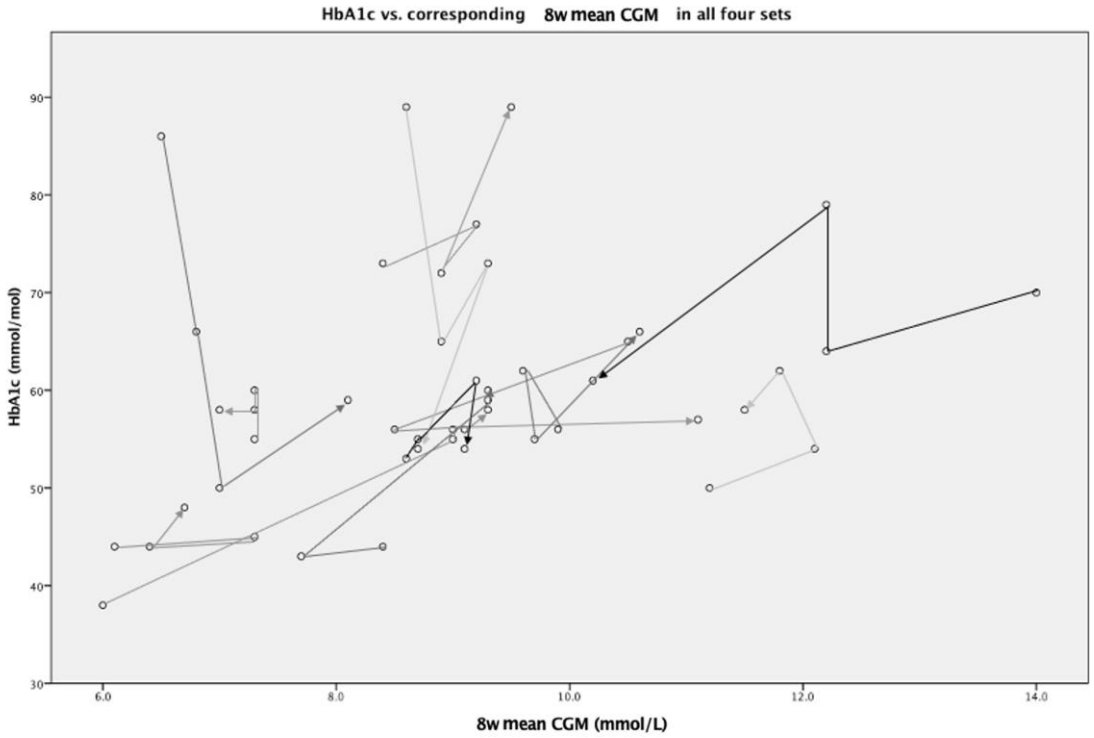

Fig. 7 Tracking over one year of HbA_{1c} (mmol/mol) vs. 8-week mean CGM (mean sensor glucose; mmol/L) in selected patients with 4 sets available. 12 children with four complete sets over the study period of one year were selected to represent individuals with at least one value far below, on or above the HbA_{1c} versus mean CGM correlation line. The figure shows four individual measurements connected by an arrow to indicate the temporal collection of HbA_{1c} and mean CGM pairs.

Discussion

Our explorative study in children with type 1 diabetes report similar Bivariate correlation coefficients between mean CGM and HbA_{1c} compared to previous reports[10,22,25], not markedly improving the correlations reported previosly using 4-8 point SMBG[5,9,10,25,26]. To our knowledge, this is the first time that mean CGM data from children using isCGM was also evaluated and we found a correlation to HbA_{1c} similar to that from rtCGM data. The clinical consequence is that a patient who presents with HbA_{1c} within the national goal may have a mean CGM ranging from above the target range to well within it. Studies on the long-term consequences of a given level of mean CGM for the development of diabetes complications is lacking. At least a better understanding of the factors that impact on how HbA_{1c} and mean CGM corresponds would help the pediatric diabetologist to interpret and discuss a potential discrepancy with the family. In the present study we found that a short diabetes duration prevents us from demonstrating any association between HbA_{1c} and mean CGM, a finding not investigated previously as Nathan et al only included adults with mean diabetes duration of 26 ±11.0 years[25]. Whether a delayed response in HbA_{1c} introduces this problem is plausible and supported by our finding of a similar problem in patients that rapidly changed their metabolic control.

Excluding patients with < 1-year diabetes duration, we identified a low HbA_{1c} and a low CGM SD and, for isCGM children, a higher

daily sensor duration to be associated with a stronger correlation between mean CGM and HbA_{1c}. We also found that HbA_{1c} was dependent on time in and degree of hyper- and hypoglycemia in isCGM children while in rtCGM children, who spend less time in hypoglycemia, only hyperglycemia impacted. A limitation of the TBR/TIR/TAR data is that the individual threshold setting was to the discretion of the individual patient and the recommendation of a lower threshold limit of 4.0 mmol/L (and not 3.9 mmol/L). However, we consider this to have minor impact on our results and it should impact less on the 'AUC' variable compared to 'number of values' variable. TIR was found to correlate with HbA_{1c} in accordance with previous compiled data from adults with Type 1 diabetes[27,28], however, with markedly lover correlation coefficient in children. TIR alone does not account for the percentage of values above or below range, both with stronger associations with HbA_{1c}. In our opinion, published data do not explain the strong emphasis on TIR in the consensus guidelines[4] on which the ISPAD Clinical Practice Consensus Guidelines[2] is largely based. The guidelines claims the existence of data demonstrating an association of TIR with later development of diabetic retinopathy in adult type 1 diabetes. Rather, these data is based on historical self reported once every 3 months, 7 points capillary glucose measurements (SMBG), distant from automatically logged 24 hour at least every minute CGM data, and the association with later complications in the DCCT[3]. At best, this is low grade evidence with minor relevance in children and adolescents.

In accordance with Nathan et al[25], we found that more data from 12 weeks prior to measuring HbA_{1c} improves the association between mean CGM and HbA_{1c} at least to some extent but beyond 8 weeks, at an average daily sensor time of above 60 %, there was little to gain. The finding that only isCGM users had a better prediction of HbA_{1c} with increasing sensor duration was not expected and should be confirmed by future studies.

Fluctuations in blood glucose indicated by CGM SD and frequency of and time in hyper- and hypoglycemia are variables that have been suggested to be of importance for long-term diabetic complications[5,10,11,22] as well as Quality of Life[29] in children with type 1 diabetes. We found that HbA_{1c} correlates to CGM SD and to time in and degree of hyperglycemia, reflected by AUC high or values above range. A correlation of HbA_{1c} to time in and degree of hypoglycemia, reflected by AUC low or values below range, was only found in isCGM children. This finding is likely to reflect that isCGM users had lower pump use and spend more time in hypoglycemia impacting significantly on HbA_{1c}. However, isCGM and rtCGM users had similar mean HbA_{1c} in accordance with previous ´trial data' showing similar HbA_{1c} in children with type 1 diabetes using insulin injections (MDI) compared to pump (CSII)[13]. In accordance with these results, a low CGM SD combined with a low HbA_{1c} in a subgroup of isCGM or rtCGM users displayed the highest correlation between HbA_{1c} and mean CGM but this subgroup analysis is hampered by the few patients in each group and the multiple regression analysis did not point to CGM SD to contribute significantly to the variation in HbA_{1c}.

Frequent sensor use was a major predictor of improving HbA_{1c} levels in previous studies[5,9,14,18] but we did not find any

correlation between these variables in our study with relatively high average sensor time. Shorter sensor duration seen in younger age-groups[5] is also consistent with our results; older children used isCGM more frequently compared to the younger rtCGM users.

Individual differences in the ability to glycate proteins have been suggested to further add to the individual variation in corresponding HbA_{1c} and mean CGM[10]. We assessed whether such a phenomenone had impact by tracking HbA_{1c} and mean CGM values over 4 consequtive sensor periods in twelve children with at least one HbA_{1c} and mean CGM pair markedly above or below that expected from the linear regression line. We expected that the individual ability to glycate would be observed as consistant tracking below or above the regression line. However, we did not find support for such a consistent tracking and thus no support that variation in an individual's ability to glycate proteins impacts on the individual association between HbA_{1c} and mean CGM. Rather, these data demonstrate that rapid changes in metabolic control disturbe the correspondance of HbA_{1c} and mean CGM data.

Our study analyze 'real life' data which may more accurately reflect how compliance and individual approaches to adjust daily blood glucose guided by real time CGM values impact on the association between HbA_{1c} and mean CGM. On the other hand the explorative and retrospective nature of the study and the lack of data on individual settings for TIR is a limitation. The number of patients studied is higher than in most previous studies and we studied children with type 1 diabetes that have not previously been studied as a group in this respect. In general, children have more variable glucose levels than adults and therefore may be expected to have more discordant HbA_{1c} and mean CGM values.

In previous studies on the correlation between HbA_{1c} and mean CGM the populations included adult patients with both type 1 and type 2 diabetes[10,22,25]. Various factors such as type of and duration of diabetes, time spent in and degree of hypo- or hyperglycemia, etc. impact on the association between HbA_{1c} and mean CMG. Some of them were identified in this study and some by others. Therefore, this study of children with type 1 diabetes – the population that most frequently uses CGM devices – is needed since many factors challenge a stable metabolic control in childhood. In children with type 1 diabetes we found that approximately 50 % (corresponding to an r= 0.7) of the variation in HbA_{1c} was explained by mean CGM with no marked difference between rtCGM and isCGM users. This modest value agrees with the r=0.74 reported by Sartore et al (19) in 68 adult type 1 or type 2 diabetic rtCGM users while Nathan et al[25] examined a smaller number of adult type 1 or type 2 diabetic patients and non-diabetic subjects and reported a higher correlation of r=0.90.

A limitation of this study is that we did not include data on the level of physical exercise and endogenous insulin production that may contribute to the association between HbA_{1c} and mean CGM. Furthermore, the analysis of potential differences between rtCGM and isCGM is hampered by the unequal distribution of CSII and MDI users among these techniques. Potentially, different CGM products may performan differently but the samle size was too small for further subgroup analys.

In conclusion, we identify factors that may help the clinician to understand why the individual mean CGM may correspond poorly with HbA_{1c}. We confirm that mean CGM is the strongest predictor of HbA_{1c} and that that at least 8 weeks of mean CGM is needed to improve prediction. However, other factors affecting this relationship should be considered. In patients with short duration of diabetes, rapid changes in metabolic control or a high CGM SD, large variations in corresponding HbA_{1c} and mean CGM values should be expected. We found that both rtCGM and isCGM give a similar prediction of HbA_{1c} although there are subtle differences in how sensor duration and AUC low impacts, which seems less likely to be explained by the methodology itself. HbA_{1c} levels are associated with long-term complications but do not alone reflect the glycemic profile of a patient, including hypoglycemic events and fluctuations in blood glucose. Therefore, daily treatment of type 1 diabetes should integrate HbA_{1c} and various CGM variables. Future studies powered to adress whether accumulating CGM variables predict acute and long-term diabetic complications are needed.

Conflicts of Interest Statement:

None

Acknowledgements Statement:

The study was supported by grants from the Research Council of Östergötaland and Barndiabetesfonden.

Funding Statement:

None

Author Contributions

Each of the authors contributed substantially to conception and design, acquisition of data, analysis and interpretation of data. They were all involved in drafting the article and revising it critically for important intellectual content and they all approve the final version to be published.

Abbreviations

AUC: Area under the curve (number times magnitude of excursions from target range)
BMI SDS: Body Mass Index Standard Deviation Score
CGM: Continuous Glucose Monitoring
CSII: Continuous Subcutaneous Insulin Infusion/ Pump
isCGM: Intermittent scanned CGM (also called Flash Glucose Monitoring)
mean CGM: Mean sensor glucose concentration measured using CGM
MDI: Multiple Daily insulin Injections
rtCGM: Real-time CGM
SMBG: Self-Monitoring of Blood Glucose
Swediabkids: Swedish national quality registry for diabetes in children and adolescents
TAR: Time above range (defined here as relative number of CGM values above 10 mmol/L in percentage)
TIR: Time in range (defined here as relative number of CGM values between 4 and 10 mmol/L in percentage)
TBR: Time below range (defined here as relative number of CGM values of 3.9 mmol or lower in percentage).

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