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The Relationship between Hemoglobin A1c and the Glucose Management Indicator and Glucose Metrics in Children and Adolescents with Type 1 Diabetes Mellitus Using Automated Insulin Delivery Systems

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What is already known on this topic?

Hemoglobin A1c (HbA1c) remains the most widely used biomarker for long-term glycemic control, but it does not fully reflect short-term glucose variability or continuous glucose monitoring systems (CGMS)-derived parameters in children with type 1 diabetes mellitus.

What this study adds?

HbA1c showed the strongest correlation with glucose management indicator (GMI) calculated over the last six weeks ($r=0.728$, $p<0.001$), suggesting that HbA1c mainly reflects recent rather than cumulative glycemic trends. GMI demonstrated stronger associations than HbA1c with key CGMS-derived metrics, including time in, above and below range [time in range (TIR), time above range and time below range, respectively]. Compared with HbA1c, GMI values were more stable across similar TIR levels, supporting its reliability for personalized diabetes management. Incorporating GMI alongside CGMS-derived parameters may provide a more accurate and clinically actionable assessment of glycemic control in pediatric automated insulin delivery users.

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ABSTRACT

Objective: Hemoglobin A1c (HbA1c) remains the standard biomarker for long-term glycemic control in type 1 diabetes mellitus (T1D), butis incapable of capturing short-term glucose variability and acute excursions. This limitation is especially relevant in children with T1D who use continuous glucose monitoring systems (CGMS) and automated insulin delivery (AID) systems. The objective of this study was to evaluate the temporal relationship between HbA1c and the glucose management indicator (GMI), and any further associations with CGMS-derived glycemic parameters over a 12 weeks in youth with T1D using AID.

Methods: This retrospective, cross-sectional, observational study, included children and adolescents with T1D using the Medtronic MiniMed 780G™ system. CGMS data covering the 12 weeks prior to HbA1c measurement were analyzed in two-week intervals. Correlations between HbA1c, GMI, and CGMS metrics were assessed.

Results: The study cohort numbered 81; 46 (57%) were female. Median age at T1D diagnosis was 8.1 (interquartile range: 4.3-10.8) years. HbA1c correlated positively with all GMI values, with the strongest correlation observed for the last six-week GMI ($r=0.728$, $p<0.001$). The mean difference between HbA1c and last 12-week GMI was 0.57% (95% confidence interval: -1.13 to 2.27). GMI demonstrated stronger correlations than HbA1c with time in range (TIR), time above range (TAR) and time below range (TBR). Notably, in individuals with similar TIR (~70%), HbA1c values varied widely (6.6-9.6%/48-81 mmol/mol), while GMI remained stable (6.8-7.1%).

Conclusion: The strongest correlation between HbA1c and the most recent 6-week GMI suggests that HbA1c reflects relatively recent glycemic trends. GMI also showed closer alignment with CGMS-derived indices such as TIR, TAR and TBR, suggesting better sensitivity in capturing day-to-day glycemic variability. We suggest GMI offers a more sensitive and clinically actionable estimate of glycemic control, supporting its integration into routine care for children with T1D using AID.

Keywords: T1D, AID, CGMS, GMI, sampling period

INTRODUCTION

Type 1 diabetes mellitus (T1D) is the most common chronic autoimmune disorder in childhood, characterized by insulin deficiency and persistent hyperglycemia. Achieving and maintaining optimal glycemic control is crucial to reduce the risk of both acute and long-term complications, particularly microvascular damage (1,2).

Glycosylated hemoglobin A1c (HbA1c) remains the primary indirect measuring method for glycemic control, and its correlation with microvascular complications is well-established (3). Although HbA1c is widely used as a predictor of glucose exposure in the three months preceding sampling, using HbA1c alone not sensitive enough to optimize and personalize treatment decisions. HbA1c cannot capture short-term glucose fluctuations or provide information about glycemic variability, hypoglycemic episodes, or postprandial excursions (3). Moreover, its accuracy may be compromised in individuals with conditions, such as anemia, iron deficiency, or hemoglobinopathies, which are not uncommon in many pediatric populations (4). The increasing use of continuous glucose monitoring systems (CGMS) systems has highlighted these limitations of HbA1c.

CGMS systems assess glucose levels in the interstitial compartment, which closely correlate with plasma glucose, thereby enabling continuous evaluation of glycemic patterns (5,6,7). CGMS provides real-time data on glucose dynamics, including time in range (TIR), time below range (TBR), time above range (TAR), and glycemic variability. In response to these advances, the glucose management indicator (GMI) was introduced to estimate average glucose levels based on CGMS data. GMI is determined using a method that generates a regression line from a plot of mean glucose concentration points on the x-axis and HbA1c values on the y-axis [calculated via the standardized formula: GMI (%)=3.318+0.006094×(mean glucose in mg/dL) or GMI (mmol/mol)=12.71+4.7058×(mean glucose in mmol/L)]. While GMI and HbA1c are intended to represent similar aspects of glycemic control, studies have shown that they often differ substantially, and this discrepancy appears to remain relatively stable for individuals over time (8). Several physiological factors contribute to the divergence between HbA1c and GMI, including interindividual differences in erythrocyte lifespan, rates of glycation, and glucose exposure. The commonly assumed erythrocyte lifespan of 120 days is not universally applicable, and newer evidence suggests that the average age of circulating erythrocytes may be significantly shorter, particularly in individuals with higher mean glucose levels.

Although a 14-day CGMS sampling period is considered sufficient to estimate glycemic patterns in adults, there is limited evidence supporting this recommendation in pediatric populations using advanced technologies such as automated insulin delivery (AID) systems. It remains unclear how well HbA1c reflects mean blood glucose (MBG) over time, and how closely GMI aligns with HbA1c and other CGMS metrics, particularly in children with T1D (9).

In this study, the objective was to examine the relationship between HbA1c and GMI, explore the temporal evolution of this relationship, and assess their associations with CGMS-derived

parameters in children and adolescents with T1D using an AID system. By analyzing biweekly CGMS data over a 12-week period, we sought to clarify the clinical relevance and reliability of these metrics in the context of modern diabetes management.

Methods

In this retrospective cross-sectional observational study, children and adolescents with T1D on Medtronic MiniMed 780G™ were enrolled. A sample size was not calculated because the study was designed to include all children and adolescents with T1D who are monitored in the Department of Pediatric Endocrinology and Diabetes, Ege University Faculty of Medicine and use AID. The data of children and adolescents with T1D who met the inclusion criteria and accepted to participate in the study were retrospectively examined during a six-month study period.

Inclusion criteria were: age between 2 and 18 years (inclusive); diagnosis of T1D for at least one year; at least six months of current use of an AID system with MiniMed 780G™- The Guardian™ Sensor (Medtronic Türkiye, İstanbul, Türkiye) (3). Exclusion criteria were: people with T1D with a diagnosis of concurrent chronic disease, including glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathies such as thalassemia or Sickle cell disease, and/or anemia of any cause.

Data for this study were obtained from a dataset approved by the Ege University Medical Research Ethics Committee (approval no.: 24-9T/38, date: 05.09.2024). This dataset was obtained retrospectively from children and adolescents with T1D using advanced hybrid closed-loop. Another study derived from this dataset discussing the temporal relationship of TIR and time in tight range (TITR) is currently in the process of being published in a journal.

The parents of all people with diabetes and from people with diabetes over 18 years of age provided written informed consent. We confirm that this study complied with the Declaration of Helsinki.

Anthropometric data (height, weight) and HbA1c levels were collected from the files of the people with diabetes. Height was measured to the nearest millimeter with Seca 264® (Seca GmbH & Co. KG, Hamburg, Germany) stadiometer and weight to the nearest 100 grams by an electronic scale (Desis Model KW®, ETS Elektronik Tartı Sistemleri, Tekirdağ, Türkiye). Standard deviation (SD) scores (SDS) for weight, height, and body mass index (BMI) were calculated, based on age and gender (10). Normal weight was defined as BMI-SDS≥-1 to <+1 for children and adolescents and a BMI of 18.5-24.9 kg/m^2 for young adults. HbA1c was measured using a turbidimetric inhibition immunoassay (TINIA, Roche cobas c513, Tina-quant HbA1c Gen.3, Roche Diagnostics Türkiye, İstanbul, Türkiye). This method is traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference system and NGSP-certified. Previous comparative studies have shown excellent agreement between the Roche TINIA method and IFCC-aligned High-Performance Liquid Chromatography (HPLC) systems for the measurement of HbA1c (r>0.98, mean bias <0.2% HbA1c).

Glucose ranges are presented in mg/dL with SI unit equivalents (mmol/L) given in parentheses. CGMS data for the entire study duration from each person with T1D were extracted from CareLink™. TIR 70-180 mg/dL, TAR>180 mg/dL, and TBR<70 mg/dL, mean glucose, mean glucose SD and CV and GMI were defined as per the 2024 international consensus guidance on TIR and other CGMS metrics (11).

Data Analysis

Six CGMS reports for the three months prior to the HbA1c measurement were obtained. For each CGMS report, a minimum sensor wear time of 80% was required. People with T1D who did not have at least five valid reports fulfilling this criterion were excluded from the study. Each report covered two-week intervals, beginning from the date of the HbA1c measurement. The first CGMS report included data from the two weeks leading up to the HbA1c measurement, the second CGMS report covered data from weeks three and four, and the third CGMS report captured data from weeks five and six. We then restructured the data to display a continuous timeline leading up to the HbA1c measurement date defined for study purposes as GMILastTwoWeeks, GMILastFourWeeks, and GMILastSixWeeks that represent the 2-, 4-, and 6-week periods immediately preceding the HbA1c measurement, respectively). A timeline diagram has been included as supplementary material to provide clearer clarification of the definitions.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). The significance level was defined as $p<0.05$. Categorical variables are represented as counts and percentages. Normal distribution of quantitative variables was assessed. Continuous variables with normal or skewed distributions are presented as mean ± SD or median [interquartile range (IQR)], respectively. Group differences were assessed using the independent t-test for normally distributed data and the Mann-Whitney U test for skewed data. We analyzed the differences in repeated measures using the repeated measures ANOVA for normally distributed data and the Friedman test for skewed data. The 12-week data from each sampling period were used to compare the values with the squared value of the Pearson correlation coefficient (R2). We evaluated the concordance between the 12 weeks of CGMS data and each of the six biweekly CGMS reports using Bland-Altman

plots and linear regression. The correlation between TIR values of GMI and HbA1c was assessed using the Williams' t-test for testing the significance of two related correlations. To control for multiple comparisons, p-values were adjusted using the Benjamini-Hochberg false discovery rate correction.

Results

The study included 81 people with diabetes; 46 (57%) were female. There were 12 (14.8%) patients with T1D who used the AID system off-label because they were under 7 years old. The median age at diagnosis was 8.1 years (IQR: 4.3-10.8), the median age at AID initiation was 11.4 years (IQR: 9.3-15.2), and the median age at the time of the study was 13.6 years (IQR: 11.3-17). At the time of AID initiation, median BMI SDS was 0.21 (IQR: -0.37/0.74). All CGMS data, with the exception of TBR, exhibited a normal distribution (Table 1).

To evaluate the reliability of our findings, a post-hoc power analysis was conducted based on the observed effect sizes. This analysis revealed a statistical power of 87% (α=0.05), indicating that the study was sufficiently powered to detect the differences observed and supporting the robustness of our results.

GMI values ($GMI_{Last\ two\ weeks}$, $GMI_{Last\ four\ weeks}$, $GMI_{Last\ six\ weeks}$, $GMI_{Last\ eight\ weeks}$, $GMI_{Last\ ten\ weeks}$, and $GMI_{Last\ twelve\ weeks}$) had a strong correlation with each other, and there was no significant difference between these correlations (p=0.26) (Table 2). HbA1c showed a strong positive correlation with all GMI values. HbA1c and $GMI_{Last\ twelve\ weeks}$/$GMI_{Last\ six\ week}$ measurements were compared using the Bland-Altman statistical method. An average difference of 0.57 units was found between HbA1c and $GMI_{Last\ twelve\ weeks}$ (95% CI: between -1.13 and 2.27, p<0.001), and average difference of 0.51 units was found between HbA1c and $GMI_{Last\ six\ weeks}$ (95% CI: between -0.61 and 1.12, p<0.001). These plots suggest that the discrepancy between these two parameters increases, particularly among individuals with poor glycemic control. A multiple linear regression analysis was performed to identify the factors influencing the difference between HbA1c and GMI values (HbA1c-GMI difference). The model was statistically significant [F(6,70)=6.43, p<0.001], explaining 35.5% of the variance (R^2=0.355, adjusted R^2=0.300). Higher TITR (β=-0.415, p=0.025) was significantly associated with a smaller HbA1c-GMI difference.

Table 1. Summary of CGM data

Number of patients: 81	Mean±SD	Median, IQR
HbA1c, %	7.26±0.67	
$MBG_{Last\ two\ weeks}$, mg/dL	139.2±12.3	
$MBG_{Last\ twelve\ weeks}$, mg/dL	140.0±11.3	
Sensor usege rate, %	90.8±8.3	
$GMI_{Last\ two\ weeks}$, %	6.6±0.29	
$GMI_{Last\ twelve\ weeks}$, %	6.6±0.25	
$TIR_{Last\ two\ weeks}$, %	77.4±7.3	
$TIR_{Last\ twelve\ weeks}$, %	76.8±7.0	
*$TBR_{Last\ two\ weeks}$, %		2 (1-4)
*$TBR_{Last\ twelve\ weeks}$, %		2 (1-4)
$TAR_{Last\ two\ weeks}$, %	17.2±4.7	
$TAR_{Last\ twelve\ weeks}$, %	16.9±5.1	
$CV_{Last\ two\ weeks}$, %	34.5±3.8	
$CV_{Last\ twelve\ weeks}$, %	35.2±4.9	

*: Non-normally distributed parameters are presented as median and IQR.
CGM: continuous glucose monitoring system; SD: standard deviation; IQR: interquartile range; HbA1C: glycosylated hemoglobin; MBG: mean blood glucose; GMI: glucose management indicator; TIR: time in range; TBR: time below range; TAR: time above range; CV: coefficient of variation

The relationship between HbA1c and $GMI_{Last\ two\ weeks}$ showed the weakest association (r=0.595, p<0.001) (Table 2). The strongest association between HbA1c and GMI was observed for the last six weeks value (r=0.728, p<0.001). The correlation of HbA1c with $GMI_{Last\ six\ weeks}$ was significantly stronger than with $GMI_{Last\ two\ weeks}$ (t=3.51; p<0.001) (Figure 1).

Table 3 summarizes the correlations between CGMS data and both HbA1c and GMI. All CGMS parameters, except for CV, showed a correlation with both HbA1c and GMI. In each of these associations, GMI exhibited a stronger correlation coefficient. The correlation between TBR and HbA1C was not significant, but both $GMI_{Last\ two\ weeks}$ and $GMI_{Last\ twelve\ weeks}$ showed a negative correlation with TBR. The correlation coefficients for the last two weeks with HbA1c and GMI indicated a significantly stronger correlation (t=2.81, df=78, p=0.014; 95% CI for r_1-r_2 = 0.05 to 0.29) between TIR and GMI (Figure 2). In cases with a TIR of approximately 70%, HbA1c levels ranged from 6.6% to 9.6%, while GMI values varied from 6.8% to 7.1%. The correlations of $GMI_{Last\ twelve\ weeks}$ with $TIR_{Last\ twelve\ weeks}$ (t=5.20, df=78, p<0.001; 95% CI for r_1-r_2=0.17 to 0.37) and $TAR_{Last\ twelve\ weeks}$ (t=6.00, df=78, p<0.001; 95% CI for r_1-r_2=0.20 to 0.40) were significantly higher than the correlation between $GMI_{Last\ two\ weeks}$ and these parameters. $TBR_{Last\ twelve\ weeks}$ showed a moderate negative correlation with both $GMI_{Last\ two\ weeks}$ (r=-0.415, p=0.007) and $GMI_{Last\ twelve\ weeks}$ (r=-0.5, p<0.001). Furthermore, no significant difference was observed between the strengths of these two correlations (p>0.47) (Table 3).

There were no clinically significant correlations between CV and HbA1c or any GMI measures (r=0.15-0.17, p=0.15-0.22).

Table 2. Correlation HbA1c and GMIs of different periods

Number of patients: 81	$GMI_{Last\ two\ weeks}$	$GMI_{Last\ four\ weeks}$	$GMI_{Last\ Six\ weeks}$	$GMI_{Last\ eight\ weeks}$	$GMI_{Last\ ten\ weeks}$	$GMI_{Last\ twelve\ weeks}$
HbA1c	r=0.595* **p<0.001***	r=0.697* **p<0.001***	r=0.728* **p<0.001***	r=0.714* **p<0.001***	r=0.718* **p<0.001***	r=0.704* **p<0.001***
$GMI_{Last\ two\ weeks}$	1	r=0.892* **p<0.001***	r=0.890* **p<0.001***	r=0.848* **p<0.001***	r=0.819* **p<0.001***	r=0.776* **p<0.001***
$GMI_{Twelve\ weeks}$	r=0.776* **p<0.001***	r=0.916* **p<0.001***	r=0.949* **p<0.001***	r=0.973* **p<0.001***	r=0.989* **p<0.001***	1

*To control for multiple comparisons, p-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction.
Reinterpreted combined datasets:
- $CGMS_{Last\ two\ weeks}$: 0 → -2 weeks
- $CGMS_{Last\ four\ weeks}$: 0 → -4 weeks
- $CGMS_{Last\ six\ weeks}$: 0 → -6 weeks
- $CGMS_{Last\ eight\ weeks}$: 0 → -8 weeks
- $CGMS_{Last\ ten\ weeks}$: 0 → -10 weeks
- $CGMS_{Last\ twelve\ weeks}$: 0 → -12 weeks
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator

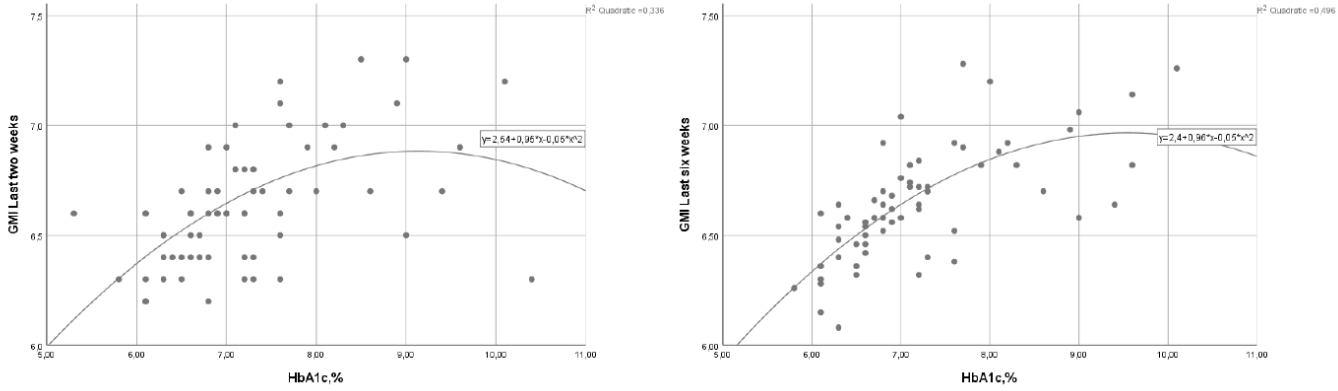

Figure 1. Comparison of HbA1c with GMILast two weeks and GMISix weeks (t=3.51; p<0.001). HbA1c shows a strong correlation with both GMILast two weeks and GMISix weeks. When these two correlations are compared using the method of testing the significance of two related correlations, it is observed that GMISix weeks correlates better with HbA1c (t=2.9, p=0.037)
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator

Table 3. Correlation HbA1c and GMI with other CGM data

Number of patients: 81	$MBG_{Last\ two\ weeks}$	$MBG_{Last\ twelve\ weeks}$	$TIR_{Last\ two\ weeks}$	$TIR_{Last\ twelve\ weeks}$	$TAR_{Last\ two\ weeks}$	$TAR_{Last\ twelve\ weeks}$	$TBR_{Last\ two\ weeks}$	$TBR_{Last\ twelve\ weeks}$	$CV_{Last\ two\ weeks}$	$CV_{Last\ twelve\ weeks}$
HbA1c	r=0.635* **p<0.001***	r=0.721* **p<0.001***	r=-0.583* **p<0.001***	r=-0.558* **p<0.001***	r=0.558* **p<0.001***	r=0.532* **p<0.001***	r=-0.12 p=0.31	r=-0.283* p=0.013	r=0.15 p=0.22	r=0.07 p=0.52
$GMI_{Last\ two\ weeks}$	r=0.993* **p<0.001***	r=0.777* **p<0.001***	r=-0.762* **p<0.001***	r=-0.473* **p<0.001***	r=0.831* **p<0.001***	r=0.605* **p<0.001***	r=-0.533* **p<0.001***	r=-0.415* **p= 0.007***	r=0.168 p=0.18	r=0.028 p=0.8
$GMI_{Last\ Twelve\ weeks}$	r=0.803* **p<0.001***	r=0.987* **p<0.001***	r=-0.647* **p<0.001***	r=-0.749* **p<0.001***	r=0.706* **p<0.001***	r=0.845* **p<0.001***	r=-0.397* **p<0.001***	r=-0.500* **p<0.001***	r=0.173 p=0.15	r=0.194 p=0.11

*To control for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction.
Reinterpreted combined datasets:
- $CGMS_{Last\ two\ weeks}$: 0 → -2 weeks
- $CGMS_{Last\ four\ weeks}$: 0 → -4 weeks
- $CGMS_{Last\ six\ weeks}$: 0 → -6 weeks
- $CGMS_{Last\ eight\ weeks}$: 0 → -8 weeks
- $CGMS_{Last\ ten\ weeks}$: 0 → -10 weeks
- $CGMS_{Last\ twelve\ weeks}$: 0 → -12 weeks
HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; CGM: continuous glucose monitoring system; MBG: mean blood glucose; TIR: time in range; TAR: time above range; TBR: time below range; CV: coefficient of variation

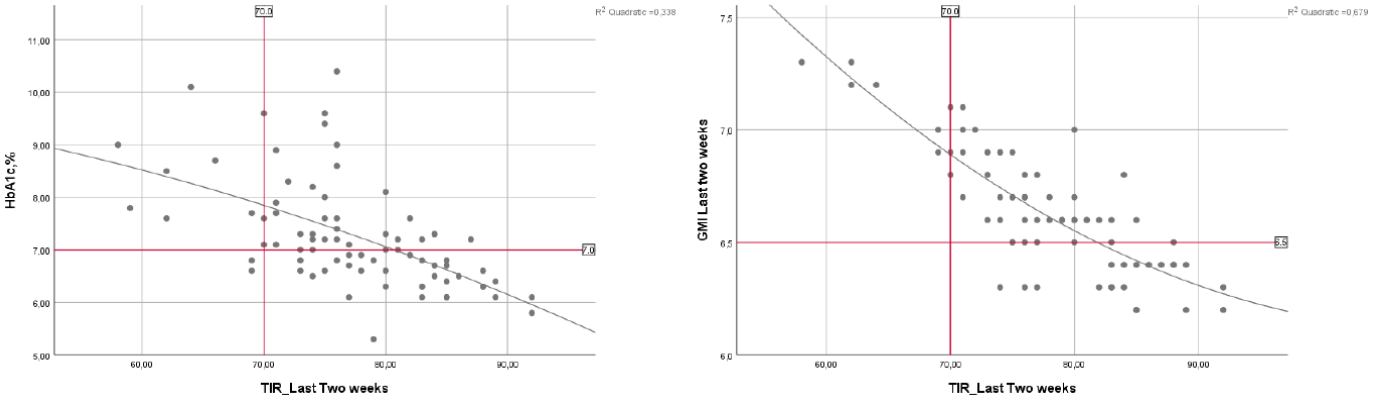

Figure 2. Comparison of TIRLast two weeks with HbA1c and GMILast two weeks (t=2.81; p=0.014). The correlation of TIRLast two weeks with HbA1c and GMILast two weeks were compared. The graph shows that TIRLast two weeks has a better correlation with GMILast two weeks (t=2.81; p=0.014)

HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; TIR: time in range

Discussion

This study demonstrated that the last six weeks of GMI correlated well with HbA1c, but the 12-week GMI exhibited a lack of similar consistency with HbA1c. GMI demonstrated a narrower variability than HbA1c and showed stronger correlations with metrics reflecting good glycemic control, such as TIR, TITR, and TBR, emphasizing its value as an indicator of optimal glycemic management.

GMI is determined using a method that generates a regression line from a plot of mean glucose concentration points on the x-axis and HbA1c values on the y-axis. Minimed Medtronic 780G™ continuous insulin infusion system calculates GMI by combining data from two trials that lasted an average of 48 days (with a range of 13 to 89 days) (3,12). The regression equation for calculating GMI (%) is 3.31+0.02392×[mean glucose in mg/dL], or GMI (mmol/mol)=12.71+4.70587×[mean glucose in mmol/L glucose]. In a study where 528 people with diabetes were included, 19% of GMI and HbA1c levels were the same, while 51% diverged by 0.3% or more, and 28% differed by 0.5%(3). In the study by Perlman et al. (13), which predominantly included adults with T1D, the discrepancy between GMI and HbA1c reached ≥0.5% in approximately half of the people with diabetes, and exceeded 1% in nearly 22%. Our data revealed a significant difference of 0.57% between HbA1c and GMI after twelve weeks, confirming the suggestion that HbA1c does not accurately reflect 12-week blood glucose in real-life conditions. Furthermore, while HbA1c exhibited a strong correlation with all GMIs, the magnitude of these correlations varied significantly (t: 3.51; p<0.001). There was a strong correlation between GMIs reflecting different periods, and there was no significant difference between the magnitude of these correlations (Table 2). Therefore, we attributed the difference in correlations between HbA1c and GMI values obtained for different periods to the fact that HbA1c did not reflect the 12-week period as well as other periods. Although numerous studies have examined the correlation between HbA1c and GMI, few have investigated how this relationship changes over time. A recent large cohort study in individuals with T1D evaluated correlations between HbA1c and CGMS data collected over last 4- and 12-week periods, demonstrating strong associations in both time frames, findings consistent with our results (14). However, because the study did not directly compare the strength of the correlations between HbA1c and the last 4- and 12-week CGMS datasets, a potential temporal difference in this relationship may have gone unnoticed. By identifying this difference, our study provides a more nuanced understanding of the time-dependent nature of the HbA1c-GMI relationship.

Several studies have suggested that the difference between GMI and HbA1c varies considerably among individuals and may be influenced by factors such as pubertal stage, the type of CGMS device used, and the mode of insulin therapy (12,13,14,15). Although no consensus has been established regarding what constitutes a clinically meaningful GMI-HbA1c discrepancy, Lenters-Westra et al. (15) recently suggested that differences of 0.8% or greater should be interpreted with caution (15). In our study, we suggest that differences of 0.55% or greater (as presented in Figure 3) should prompt more cautious interpretation of glycemic control.

$GMI_{Last\ six\ weeks}$ showed the strongest correlation with HbA1c, suggesting that blood glucose significantly influenced circulating red blood cells in the final six weeks. The fact that HbA1c did not consistently reflect the 12-week period lends credence to the hypothesis that GMI reflects temporal changes in average blood glucose better than HbA1c. The literature shows that the

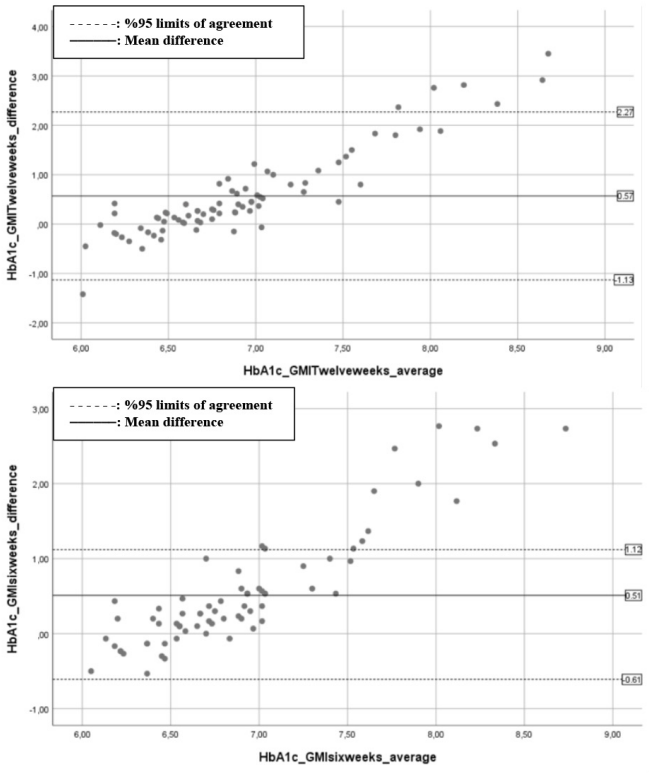

Figure 3. Comparing HbA1c and GMItwelve weeks and GMIsix weeks with the Bland-Altman Plots test. HbA1c and GMItwelve weeks / GMIsix week measurements were compared using the Bland-Altman statistical method. Average difference of 0.57 units was found between HbA1c and GMItwelve weeks (95% CI: between -1.13 and 2.27, p<0.001), and average difference of 0.51 units was found between HbA1c and GMIsix weeks (95% CI: between -0.61 and 1.12, p<0.001). These plots suggest that the discrepancy between these two parameters increases particularly among individuals with poor glycemic control

HbA1C: glycosylated hemoglobin; GMI: glucose management indicator; CI: confidence interval

difference between HbA1c and GMI remains relatively constant for each individual over time, possibly due to the individuals having a different erythrocyte lifespan or erythrocyte glycation rate than the average, making GMI useful in personalized diabetes treatment (3,8,16). Recent research has shown that erythrocyte lifespan varies greatly, even in healthy people (17,18,19). The homogenous erythrocyte survival model, which predicts an erythrocyte lifespan of about 120 days, has led to a misunderstanding of HbA1c. Beltran Del Rio et al. (20) created HbA1c-MBG curves with the probability of maximum erythrocyte lifespan (MEL) in circulation being 90-117 and 140 days. Individuals with higher MBG have a shorter MEL (90 days), whereas those with lower MBG have a longer MEL (140 days). The authors interpreted this as hyperglycemia having a shortening effect on erythrocyte lifetimes, leading to clinically significant variations in HbA1c interpretation. They also suggested that the variability in HbA1c at the same MBG value may be larger than previously reported (19). Cohen et al. (16) found that while the MEL was 117±12 days, the average lifespan of erythrocytes was 80±11 days, much shorter than the widely recognized 120 days. They presented this as evidence that age does not affect the clearing of erythrocytes from circulation. The study found that age-related clearance accounted for only 38±9.6% of erythrocytes from circulation and reached MEL. The average age of circulating erythrocytes was 49±6 days, and the authors estimated the HbA1c half-life to be 25-35 days (16). A lot of people agree that the changing relationship between HbA1c and MBG is due in part to reticulocyte glycation in the bone marrow, the rate at which glucose separates from hemoglobin, and how high blood sugar affects the lifespan of circulating erythrocytes (16,20). In our study, HbA1c had the strongest correlation with $GMI_{Last\ six\ weeks}$, which is consistent with the findings of these two studies. The finding that HbA1c shows the strongest correlation with the last 6-week data will contribute to the interpretation of which time frame for glycemic control HbA1c may best reflect in routine clinical practice. In addition, it will raise the discussion on the clinical value of evaluating 6-week CGM data instead of 2-week CGM data.

Many investigations have demonstrated that, despite a strong association between TIR and HbA1c, a wide range of HbA1c for the same TIR value leads to inaccurate case prediction (21,22). Bosoni et al. (22) observed that a lower TIR maintained the HbA1c ≤7% in a subgroup of patients whereas another subgroup needed a high TIR to achieve the same result. In our study, given identical TIR values, HbA1c had a substantially broader distribution than GMI. We interpret this to show that human factors have less influence on GMI, allowing GMI to predict the TIR within a tighter range. Furthermore, as shown in Figure 3, the widening gap between GMI and HbA1c in individuals with suboptimal glycemic control further illuminates the necessity of personalized diabetes management using CGMS data, particularly GMI, in this population. As demonstrated in the present study, GMI correlates more strongly with TIR, TAR, and TBR than HbA1c, indicating that GMI is superior to HbA1c in measuring glycemic control. Though the use of CGMS technology in children with T1D is increasing, the efficient use of CGMS data remains low (23). This is primarily due to the difficulty in interpreting CGMS data and the lack of standardization (24). To achieve consistency, a recently published international agreement on the use of CGMS proposed that CGMS be sampled for 10 to 14 days, with glycemic control targets of TIR>70%, TAR<25%, and TBR<4% (9,25). Based on research indicating that a longer sampling period does not increase correlation, this guideline recommended a 14-day sampling period. However, it's important to note that these studies primarily involved adults with diabetes with minimal use of insulin infusion pumps. Several studies have found that a 14-day sampling interval might be highly deceptive, especially when monitoring hypoglycemic objectives (26,27,28). In our study,

GMI data from CGMS reports from different sampling periods revealed a significant correlation. However, $TIR_{Last\ twelve\ weeks}$ and $TAR_{Last\ twelve\ week}$ had differing levels of correlation with $GMI_{Last\ two\ weeks}$ and $GMI_{Last\ twelve\ weeks}$, highlighting the need to evaluate the reliability of the 14-day sampling period.

Another area in which CGMS shows a clear advantage over HbA1c is its ability to facilitate remote monitoring through telemedicine, thereby enabling more frequent and responsive evaluation of glycemic control. During the coronavirus disease-2019 pandemic, Kaushal et al. (29) observed significant improvements in mean CGMS glucose and GMI among youth with T1D despite a reduction in face-to-face encounters. In addition, Plachy et al. (30) demonstrated that telemedicine follow-up was non-inferior to traditional in-person visits for maintaining glycemic outcomes, while allowing continuous assessment of CGMS-derived indices such as TIR. Moreover, Ferber et al. (31) reported short-term improvements in TIR and GMI following both telemedicine and on-site consultations, showing the stability of glycemic management when CGMS data are accessible remotely. Collectively, these findings suggest that CGMS metrics, particularly GMI, enable real-time remote evaluation and timely treatment adjustments, an advantage that is inherently absent in HbA1c-based assessment.

Study Limitations

This study has limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Second, all individuals were using the same AID system, and results may not extend to those using other insulin delivery methods. Although HbA1c was measured using the TINIA method rather than HPLC, both assays are IFCC-aligned, and their results are considered interchangeable within clinically acceptable limits. Therefore, potential assay-related bias is unlikely to have affected the main findings.

Conclusion

Our findings further highlight the limitations of HbA1c as a standalone measure of glycemic control in children and adolescents with T1D, particularly those using AID systems. Although HbA1c remains a widely available and used clinical tool, its variability and limited sensitivity to glycemic fluctuations reduce its reliability for personalized diabetes care. In contrast, GMI, derived from CGMS data, demonstrated more stable and consistent associations with key glycemic metrics, including TIR and TITR. GMI was less influenced by physiological variability and more accurately reflected recent glucose exposure, particularly over the six- to twelve-week period.

Incorporating GMI and other CGMS-based metrics into routine clinical assessment may enhance treatment decisions and optimize outcomes, especially in pediatric populations using advanced diabetes technologies. Future guidelines should consider greater emphasis on CGMS-derived measures alongside or in place of HbA1c to support individualized, data-driven management strategies in T1D.

Ethics

Ethics Committee Approval: Data for this study were obtained from a dataset approved by the Ege University Medical Research Ethics Committee (approval no.: 24-9T/38, date: 05.09.2024).

Informed Consent: The parents of all people with diabetes and from people with diabetes over 18 years of age provided written informed consent.

Footnotes

Prior Presentation: This study was presented at the Turkish National Pediatric Endocrinology Congress in May 2024.

Availability of Data and Materials: The datasets generated and analyzed during the current study are not publicly available due to institutional and ethical restrictions but are securely stored on the personal computers of the corresponding author (Damla Gökşen) and co-author (Emrullah Arslan). The de-identified summary dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Authorship Contributions

Surgical and Medical Practices: Emrullah Arslan, Deniz Özalp Kızılay, Damla Gökşen, Concept: Emrullah Arslan, Samim Özen, Şükran Darcan, Damla Gökşen, Design: Emrullah Arslan, Samim Özen, Şükran Darcan, Damla Gökşen, Data Collection or Processing: Emrullah Arslan, Hanife Gül Balkı, Günay Demir, Damla Gökşen, Analysis or Interpretation: Emrullah Arslan, Günay Demir, Samim Özen, Şükran Darcan, Literature Search: Emrullah Arslan, Hanife Gül Balkı, Deniz Özalp Kızılay, Writing: Emrullah Arslan, Damla Gökşen.

Conflict of Interest: Two authors of this article, Samim Özen and Damla Gökşen, are member of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, they did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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