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RESEARCH LETTER

WILEY

Time in tight range in automated insulin delivery system users: Real-world data from children and adolescents with type 1 diabetes

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1 | BACKGROUND

Since their introduction into daily clinical practice, automated insulin delivery (AID) devices have yielded significant benefits for people with type 1 diabetes (T1D), improving glycaemic outcomes.[1,2] Indeed, these devices can facilitate the achievement of clinical targets for continuous glucose monitoring (CGM) metrics with time in range (TIR) above 70% and consistently flat glycaemic levels, prompting the redefinition of glycaemic goals.[3]

Time in tight range (TITR), that is, the percentage of time spent in the target glucose range 3.9–7.8 mmol/L (70–140 mg/dL), is a promising novel CGM glycaemic metric. According to recent evidence, TITR could shortly become a core CGM metric to assess glycaemic outcomes and the risk of diabetes complications,[4] particularly in AID users. However, more data about this novel metric are currently needed. Thus, this study aimed to evaluate real-world TITR data in a large cohort of children and adolescents with T1D using AID systems.

2 | METHODS

This cross-sectional study collected clinical and real-world CGM data from children and adolescents with T1D followed in 28 Italian paediatric diabetes centres during quarterly follow-up outpatient visits. Inclusion criteria were age between 6 and 18 years, diagnosis of T1D according to International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines,[5] and at least 6 months of current use of AID systems (Medtronic Minimed™ 780G, or Tandem t:slim X2™ Control IQ). Exclusion criteria were the partial remission phase according to the Hvidovre Study definition,[6] CGM sensor use <70%, chronic diseases, and use of drugs interfering with glycaemic levels. The study protocol was approved by the Ethics Committee of Messina University (n. 39–23). Informed content was obtained from all study participants' parents. Demographic and clinical data, namely, age, gender, diabetes duration, anthropometric parameters including standardized body mass index (BMI), CGM device and AID system use, total daily insulin dose (TDD; units $\times$ kg^{-1} $\times$ day), and glycated haemoglobin (HbA1c) values were collected at enrolment.

The CGM data from the 2-week pre-visit period were gathered using specific web-cloud platforms (i.e., CareLink® Professional software, Diasend®, Glooko®Web) with calculation of the following CGM metrics: mean glucose and its standard deviation (SD), percentage of TIR 3.9–10.0 mmol/L (70–180 mg/dL), percentage of TITR 3.9–

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7.8 mmol/L (70–140 mg/dL), percentage of time above range (TAR) > 10 mmol/L (180 mg/dL), percentage of TAR 10.1–13.9 mmol/L (181–250 mg/dL; TAR_1), percentage of TAR > 13.9 mmol/L (250 mg/dL; TAR_2), percentage of time below range (TBR) < 3.9 mmol/L (70 mg/dL), percentage of TBR 3.0–3.9 mmol/L (54–70 mg/dL; TBR_1), percentage TBR < 3 mmol/L (54 mg/dL; TBR_2), glucose management indicator, coefficient of variation (%CV), glycaemia risk index (GRI).

Descriptive statistics are reported as mean (SD). Categorical data are presented as count (*n*) and percent values (%). Parametric tests were applied since the numerical variables were normally distributed according to the Kolmogorov–Smirnov test. Participants were categorized into four subgroups based on TITR interquartile ranges, and differences among subgroups were evaluated using the one-way analysis of variance test, followed by post hoc least square difference and chi-squared tests for subgroup comparisons, as appropriate. Univariate and multivariate linear regression models were performed to identify significant predictors of TITR values with age, BMI z-score, gender, diabetes duration, TDD, automatic mode use (%), and number of different insulin-to-carbohydrate ratios (ICRs) as covariates. A p value <0.05 was taken to indicate statistical significance. All the analyses were performed using SPSS v.22.0 (SPSS, USA, Chicago, IL, USA).

3 | RESULTS

A total of 613 children and adolescents (mean age 12.7 ± 3 years, diabetes duration 5.6 ± 3.6 years, 49.3% females) participated in the study. Demographic variables, anthropometric variables, insulin therapy, and glycaemic metrics of the total sample and according to TITR quartiles are shown in Table 1. More than half of the study participants (53.7%) were Medtronic Minimed™ 780G users, and the remaining (46.3%) used Tandem t:slim X2™ Control IQ. Clinical characteristics, specific systems' settings and CGM metrics according to advanced hybrid closed-loop systems are shown in Supplemental File 1.

The average TITR was 47.4% ± 11.8%, and 43.9% of study participants achieved TITR > 50%. No significant differences in age, diabetes duration, BMI, BMI z-score, or TDD were detected among subgroups. Medtronic Minimed™ 780G users showed higher TITR levels than individuals using Tandem t:slim X2™ Control IQ (51.1% vs. 43.3%; $p < 0.001$ [Supplementale File 1; Supplemental File 2]).

Figure 1 shows the distribution of TIRs among the four TITR quartile subgroups and the overall study cohort. All glycaemic metrics demonstrated significant improvements with increasing TITR ($p < 0.001$ for all metrics), except for TBR. Several significant pairwise differences between TITR quartile subgroups were also observed. Notably, TIR to TITR ratio was inversely associated with TITR levels, ranging from 1.87 in the first TITR quartile to 1.34 in the fourth TITR quartile.

Multivariate regression analysis revealed that time spent in automatic mode ($B = 0.265$, 95% confidence interval (CI) 0.081–0.450; $p = 0.005$) and the number of different ICRs ($B = 1.244$, [95% CI 0.294–2.195]; $p = 0.010$) were significant predictors of TITR ($R^2 = 0.045$), adjusting for age, diabetes duration, gender, BMI z-score and TDD (Supplemental File 3). The results of the multivariable model remained unchanged, with the number of ICRs continuing to be significant, even after including the AID system as an independent variable.

4 | CONCLUSIONS

This study showed that the mean TITR measured in a large cohort of paediatric AID users was 47.8%. This result aligns with a recent analysis among over 10 000 adults with T1D using the Minimed™780G system, showing a mean TITR of 48.8%.[4] As TITR is a relatively new CGM metric, a consensus on its recommended goal has not yet been established. Some researchers have proposed a TITR target of >50% as a treatment goal for AID users.[7] A previous Swedish study in youths with T1D suggested that achieving a TITR of 50% corresponds to an HbA1c value of 48 mmol/mol.[8] A recent single-centre real-world study reported a mean TITR of 60.2% in a cohort of 56 children and adolescents using an advanced hybrid closed-loop system.[9] However, findings from other investigations demonstrate that AID therapy typically results in an average TITR of approximately 45% in paediatric individuals, including preschool-aged children.[10,11] Accordingly, in our study, fewer than half of the participants achieved the threshold.

Our findings demonstrate that higher TITR levels are associated with significantly better glycaemic parameters, including CV and GRI, which reflect short-term glucose variability and the clinical risk related to the frequency and severity of glycaemic fluctuations.[12] Consequently, TITR emerges as a crucial marker for optimizing glucose control, especially in children with T1D, considering their long life expectancy and the relevance of metabolic memory.[13] To support this theory, a recent retrospective cross-sectional real-world study reported an inverse association between TITR and the presence of microvascular complications and cerebrovascular accidents in people with T1D.[14]

It is important also to note that TBR levels significantly increased across TITR quartiles. However, the mean TBR values in the third and fourth quartiles were 3.2% and 3.4%, respectively, which fall within the recommended target for time spent in hypoglycaemia. Our analysis outlines a significant reduction in the TIR-to-TITR ratio as TITR increases, further addressing the non-linear solid correlation between these two metrics already reported by Beck et al.[15] These authors also found that the TIR–TITR relationship varies according to CV and TBR, such that higher CV or TBR values correspond to higher TITR for a given TIR,[16] supporting our results regarding the change of CV and TBR values across TITR quartiles.

Multiple regression results are consistent with previous studies, emphasizing the importance of using the automatic mode for the majority of time to ensure optimal glycaemic outcomes.[17] Interestingly, the number of ICRs emerged as an additional predictor of TITR. This finding highlights the critical importance of using the most appropriate ICR for each meal, especially during childhood. When determining ICR, several factors should be considered, including the variation in insulin sensitivity throughout the day and the glycaemic index values of commonly consumed foods.[18]

To our knowledge, this variable still needs to be explored in depth, and our findings suggest a better assessment of the impact of this specific device setting on AID users.

TABLE 1 Clinical characteristics and continuous glucose monitoring metrics according to TITR quartile. Data are presented as mean (standard deviation of the mean) and absolute frequencies (percentages).

	Time in tight range 70–140 mg/dl					
	1st quartile <40% (*n* = 153)	2nd quartile 40%–48% (*n* = 153)	3rd quartile 48%–55% (*n* = 154)	4th quartile >55% (*n* = 153)	*p*-value	Overall (*n* = 613)
Age (years)	12.2 (3.1)	12.7 (3.2)	12.4 (2.8)	12.8 (2.8)	0.700	12.6 (2.9)
Sex						
Male	81 (52.9)	80 (52.3)	76 (49.4)	74 (48.4)	0.824	311 (50.7)
Female	72 (47.0)	73 (47.7)	78 (50.6)	79 (51.6)		302 (49.3)
Diabetes duration (years)	5.3 (3.8)	5.3 (3.6)	5.1 (3.5)	4.5 (3.2)	0.225	5.6 (3.6)
BMI	21.1 (3.8)	21.2 (3.9)	20.5 (3.9)	21.0 (3.5)	0.310	21.0 (3.8)
BMI z score	0.62 (1.3)	0.62 (0.99)	0.46 (1.1)	0.51 (0.89)	0.491	0.55 (1.1)
TDD (units × kg^{-1} × day)	0.90 (0.22)	0.87 (0.22)	0.85 (0.20)	0.86 (0.23)	0.313	0.86 (0.23)
Basal insulin delivery (%)	46.5 (9.6)	45.3 (9.0)	42.3 (8.8)	40.2 (8.6)	<0.001§	43.6 (9.3)
Bolus insulin delivery (%)	53.5 (9.6)	54.7 (9.0)	57.7 (8.8)	59.8 (8.6)	<0.001§	56.4 (9.3)
HbA1c (mmol/mol)	54 (16)	51 (16)	50 (15)	46 (15)	<0.001*	51 (16)
HbA1c (%)	7.1 (0.69)	6.8 (0.65)	6.7 (0.55)	6.4 (0.56)	<0.001*	6.8 (0.67)
TIR (%)	58.8 (8.3)	69.9 (5.0)	75.6 (4.8)	83.1 (4.8)	<0.001*	71.9 (10.6)
TIR to TTR ratio	1.9 (0.27)	1.6 (0.12)	1.5 (0.09)	1.3 (0.08)	<0.001*	1.6 (0.25)
TBR (%)	1.5 (1.3)	2.3 (1.8)	3.2 (2.5)	3.4 (2.5)	<0.001**	2.7 (2.2)
TBR_1 (%)	1.1 (0.99)	1.8 (1.3)	2.4 (1.7)	2.7 (1.8)	<0.001**	2.0 (1.6)
TBR_2 (%)	0.76 (0.54)	0.77 (0.63)	1.16 (0.91)	1.21 (0.93)	<0.001***	0.92 (0.78)
TAR (%)	39.9 (8.2)	27.9 (5.1)	21.4 (4.5)	13.6 (4.6)	<0.001*	25.6 (11.2)
TAR_1 (%)	27.1 (4.6)	21.1 (3.8)	17.2 (2.9)	11.6 (3.3)	<0.001*	19.23 (6.8)
TAR_2 (%)	12.9 (6.6)	6.8 (3.5)	4.1 (2.8)	1.9 (1.8)	<0.001*	6.39 (5.6)
CV (%)	34.8 (4.9)	35.4 (5.3)	35.6 (5.5)	32.8 (4.4)	<0.001§	34.67 (5.2)
Mean sensor glucose (mg/dl)	177.5 (18.5)	157.1 (11.0)	146.5 (11.2)	133.1 (8.0)	<0.001*	153.3 (20.6)
Mean sensor glucose (mmol/L)	54.4 (7.6)	51.0 (7.1)	50.0 (6.1)	47.6 (6.1)		8.4 (1.1)
SD sensor glucose (mg/dl)	62.1 (11.7)	56.0 (9.3)	52.6 (9.5)	43.5 (6.9)	<0.001*	53.4 (11.6)
SD sensor glucose (mmol/L)	3.4 (0.04)	3.1 (0.04)	2.9 (0.04)	2.4 (0.04)		2.9 (0.64)
GMI (%)	7.5 (0.44)	7.0 (0.23)	6.8 (0.18)	6.5 (0.20)	<0.001*	6.9 (0.48)
GRI	45.6 (11.9)	32.9 (8.0)	28.1 (8.3)	20.6 (7.6)	<0.001*	31.7 (12.9)
Automatic mode use (%)	94.5 (5.9)	95.1 (5.7)	95.1 (5.9)	96.7 (4.5)	0.006§	95.4 (5.6)
Number of daily ICRs						
% Participants using <2 different ICR	60 (39.2)	51 (33.3)	36 (23.4)	44 (28.8)	0.054	191 (31.1)
% Participants using 2 to 4 different ICR	49 (32.0)	45 (29.4)	49 (31.8)	49 (32.0)		192 (31.3)
% Participants >4 different ICR	44 (28.8)	57 (37.3)	69 (44.8)	60 (39.2)		230 (37.5)

Abbreviations: BMI, body mass index; CV, coefficient of variation; GMI, glucose management indicator; GRI, glycaemic risk index; ICR, insulin to carbohydrate ratio; SD, standard deviation of mean glucose; TAR, time above range >10 mmol/L; TAR_1, time above range 10.1–13.8 mmol/L; TAR_2, time above the range >13.9 mmol/L; TBR, time below range <3.9 mmol/L; TBR_1, time below range 3–3.8 mmol/L; TBR_2, time below range <3 mmol/L; TDD, total daily insulin dose; TIR, time in range 3.9–10 mmol/L; TITR, time in tight range 3.9–7.8 mmol/L.

*All the TITR quartile subgroups were significantly different from each other.

**The 3rd quartile and 4th quartile were not significantly different from each other.

***1st quartile and 2nd quartile were not significantly different from each other.

§1st and 2nd quartiles were not significantly different, and the 2nd and 3rd quartiles were not significantly different.

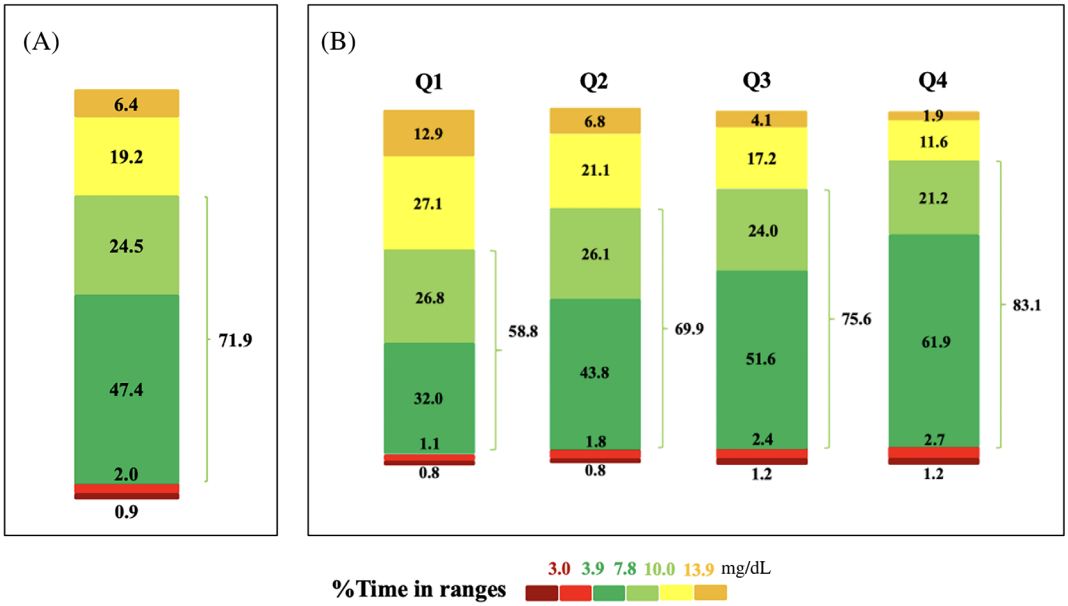

FIGURE 1 Key continuous glucose monitoring time in range (TIR) metrics, including TIR 3.9–10 mmol/L (70–180 mg/dL; dark and light green segments combined), time in a tight range (TITR) 3.9–7.8 mmol/L (70–140 mg/dL; darker green segment), and TIR 7.8–10 mmol/L (140–180 mg/dL; lighter green), in the overall study cohort (A), and the four TITR quartiles subgroups (B).

The main limitation of this study was the inclusion of subjects using two AID algorithms that operate differently. Consequently, the analysis did not include certain potential variables, such as specific setting modes and distribution between basal and bolus delivery. Additionally, the use of different CGM systems represents a weakness, compounded by the lack of raw glucose data. Furthermore, the baseline TITR was not included in the regression models due to the cross-sectional design of the study. Despite these limitations, the primary strength of this study lies in its large and well-characterized paediatric cohort.

In conclusion, this study provides new, additional insights regarding evaluating glycaemic profiles of children and adolescents with T1D using AID systems, emphasizing how TITR can complement the information offered by TIR alone.

AUTHOR CONTRIBUTIONS

Stefano Passanisi and Claudia Piona conceptualized the study and wrote the first draft of the paper. Bruno Bombaci and Valentina Mancioppi collected the data. Giuseppina Salzano, Anita Morandi and Marco Marigliano reviewed and edited the manuscript. Claudio Maffeis and Fortunato Lombardo contributed to the discussion and reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Stefano Passanisi received speaking honoraria from Roche and Movi SpA. Giuseppina Salzano received speaking honoraria from Lilly. Marco Marigliano received speaking honoraria from Novo Nordisk. Bruno Bombaci reports a grant from Abbott. Fortunato Lombardo received a speaking honorarium from Movi SpA; he is an advisory board member of Sanofi. Claudio Maffeis received consultancy fees from Novo Nordisk for his role as a member of the ACTION Teens Steering Committee during the conduct of the study; he also reports honoraria (for lectures) from Eli Lilly, Novo Nordisk, Roche and Sanofi, and participation in advisory boards for Abbott, Eli Lilly, Medtronic and Sanofi outside the submitted work. All other authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15791.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (S.P.).

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SUPPORTING INFORMATION

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

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APPENDIX A

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