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Identifying the relationship between CGM time in range and basal insulin adherence in people with type 2 diabetes

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Abbreviations: Continuous Glucose Monitor (CGM), Time in Range (TIR), Type 1 Diabetes (T1D), Type 2 Diabetes (T2D)

Keywords: Adherence, connected insulin pen, insulin dosing data, insulin therapy, Type 2 diabetes

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Abstract

Background: The study aimed to determine the relationship between basal insulin adherence and glycemic control evaluated by Time in Range (TIR) in people with insulin-treated type 2 diabetes (T2D), using data from both continuous glucose monitors (CGM) and connected insulin pens. Furthermore, the study aimed to determine the best basal insulin adherence metric.

Method: CGM data and basal insulin data were collected from 106 insulin-treated people (aged ≥18 years) with T2D. Three different adherence metrics were employed (dose deviation, dose deviation ≤20%, and a traditional metric) and a three-step methodology was used to measure insulin adherence level. The coefficient of determination (r^2), based on a univariate linear regression analysis, was used to determine the relationship between each adherence metric and TIR.

Results: A statistically significant relationship was observed between TIR and adherence quantified as the dose deviation ≤20% metric ($R^2 = 0.67$, $p = 0.006$). Neither the relationship between the dose deviation metric and TIR ($R^2 = 0.43$, $p = 0.08$) nor the relationship between the traditional metric and TIR ($R^2 = 0.35$, $p = 0.23$) was found to be statistically significant.

Conclusions: Our study indicates a relationship between basal insulin adherence and TIR in people with insulin-treated T2D. This seems to underscore the role of basal insulin adherence for optimal glycemic outcomes and utilizing TIR as a clinical marker. Further, the results suggest that the magnitude of deviation from the recommended basal insulin dose impacts glycemic control, indicating dose deviation ≤20% as a more accurate metric for quantifying adherence.

1. Background

For decades, research has shown that glycemic control is one of the most important goals for maintaining the health of people with type 2 diabetes (T2D) [1]. Glycemic control is strongly correlated with macrovascular and microvascular complications [2], while also being associated with higher healthcare costs [3], and higher utilization of healthcare services [4].

Despite the development of new drugs, insulin therapy remains a key component for glycemic control for many people with T2D [5]. However, many struggle to maintain their insulin regimen over time [6]. They may forget or skip doses or administer greater or lesser amounts of insulin than recommended [7]. Insulin non-adherence and difficulties with insulin dosing have been shown to result in suboptimal glycemic control in people with T2D [8–10], with less than half of individuals treated with basal insulin alone or combined with oral antidiabetic agents achieving an HbA1c target of <7.0% [11,12].

The HbA1c test has typically been used for the evaluation of glycemic control [13]; nevertheless, recent research lean towards Time in Range (TIR) as a more valid clinical metric for evaluating glycemic control [14]. TIR expresses the percentage of the time a person spends within their target glycemic range of 3.9-10.0 mmol/L measured using a Continuous Glucose Monitor (CGM). TIR offers a comprehensive view of glycemic control by capturing daily blood glucose fluctuations, contrasting HbA1c, which reflects average glycemic levels over three months [14]. Ekberg et al. demonstrated a relationship between missed basal insulin injections and CGM outcomes (including TIR) in people with type 1 diabetes (T1D) [15,16]. More recently, Danne et al. (2024) found an association between adherence to a basal-bolus insulin regimen and glycemic outcomes, including TIR, using real-world observational data collected through smart insulin pens in a diverse population of people with diabetes across 16 countries [17].

In addition to introducing TIR as a novel metric for evaluating glycemic control, prior research delved into the correlation between glycemic control and adherence, the latter defined by instances of missed or forgotten doses [6,7,18,19]. However, we suggest that the magnitude of deviation from the recommended basal insulin dosage holds importance for glycemic control in people with insulin-treated T2D. For a person with a recommended dose of 25 units, deviating by 1 unit would yield a lesser impact than a deviation of 20 units [20]. Standard adherence measures commonly used haven't allowed for including the dose deviation; however, with the introduction of connected insulin pens data for this is now possible [7].

This study therefore aimed to determine the relationship between basal insulin adherence and glycemic control evaluated by TIR in people with insulin-treated T2D, using data from both CGM and connected insulin pens. Furthermore, the study aimed to determine the best basal insulin adherence metric for people with insulin-treated T2D.

2. Methods

2.1 Data collection

Basal insulin and CGM data for the present study were provided from 106 participants randomized to the intervention group of the DiaMonT trial (NCT04981808); an open-labelled randomized controlled trial. The trial investigated the effect of telemonitoring on glycemic control for people with T2D and has previously been described in detail by Hangaard et al. [21]. Enrolled participants were ≥18 years of age, had a confirmed diagnosis of T2D for a minimum duration of one year, and were treated with basal insulin only or in combination with bolus insulin.

Basal insulin injection data were collected from participants using a connected insulin pen (NovoPen6, Novo Nordisk A/S) for insulin administration. All participants were treated with insulin degludec. The connected insulin pen administered insulin in 1-unit dose increments with a maximum dose of up to 60 units. The connected insulin pen

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automatically recorded the time, date, and number of units for each injection [22]. Participants were instructed to transfer injection data to their smartphones at least once a week. In cases where a participant failed to transfer the data, trial personnel would remind them; no other forms of reminders were provided. Trial personnel registered recommended basal insulin dose data, including baseline doses and any continuous adjustments made throughout the trial. Insulin dose adjustments were managed by clinicians, and participants were instructed not to make any self-titrations. Participants had their glycemic control monitored using a real-time CGM device (G6, Dexcom) for the entire trial period.

2.2 Preprocessing

Data from weeks 2 to 11 of the trial were included in the analysis. Basal insulin injection data were structured into 24-hour periods from 03:00 to 03:00 the next day. Doses recorded on the same day were summed and doses of ≤2 units were excluded. The exclusion was performed because participants were instructed to test the insulin flow with a 2-unit air shot after replacing the insulin cartridge [22]. If no insulin injection was recorded by the connected insulin pen on a given day, 0 units were imputed. CGM data were structured into 24-hour periods from midnight to midnight the next day. To account for the pharmacokinetic characteristics of insulin degludec, which is characterized by a steady-state duration of 72 hours [23], a forward shift of +3 days was applied to the adherence level data. For example, adherence level on day one impacts TIR on day four, see Figure 1. This adjustment ensured that the corresponding CGM data for a given day was aligned with the insulin degludec steady-state period.

Before shift:

	Day 1	**Day 2**	**Day 3**	Day 4	Day 5	Day 6
TIR	76.3	88.7	80.2	77.1	41.4	69.4
Adherence level	**97.9***	**75.1***	**80.9***	97.4	83.9	95.6

+3 days shift:

	Day 1	Day 2	Day 3	**Day 4**	**Day 5**	**Day 6**
TIR	76.3	88.7	80.2	77.1	41.4	69.4
Adherence level				**97.9***	**75.1***	**80.9***

Figure 1. Illustration of the +3 days forward shift applied to adherence level data to align with the pharmacokinetic profile of insulin degludec.

2.3 Outcomes

Adherence

A novel three-step method, described in detail elsewhere, was used to measure adherence [7]. The recommended basal insulin doses were compared to the basal insulin doses recorded by the connected insulin pen each day. A correct dose was defined as a recorded dose equivalent to the recommended dose, while an increased dose referred to a recorded dose exceeding the recommended dose, and a reduced dose indicated a recorded dose smaller than the recommended dose. A missed dose was defined where 0 units were imputed.

Three adherence metrics were employed to quantify daily adherence. The first metric, dose deviation, quantified adherence as the percentage difference between the administered dose and the recommended dose on a given day. The second metric, dose deviation ≤20%, inspired by Sokol et al. [20] which associated adherence levels of ≥80% with improved health outcomes, quantified adherence as a daily dose deviation of ≤20%. The third metric, the traditional metric, was based on standard adherence measures and quantified adherence as administering the recommended dose and nonadherence as any deviation from it.

Example of adherence level calculation:

On a given day, the recommended dose for a participant was 45 units, but only 40 units were administered, as recorded by the connected insulin pen. Thus, the participant administered five units less than recommended, resulting in an absolute percentage difference of 11%. The adherence level based on the three metrics would be as follows:

- *Dose deviation*: The participant has an adherence level of 89% on the given day as he/she deviated 11% (100% – 11% = 89%).
- *Dose deviation* ≤20%*:* The participant is considered adherent on this day as the deviation from the recommended dose was ≤20%.
- *Traditional metric,* the participant is considered non-adherent as the administered dose deviated from the recommended dose.

Glycemic control

Glycemic control was evaluated using CGM TIR. TIR was defined as the time spent with sensor glucose within the acceptable range (3.9 – 10 mmol/L) per day. TIR values were calculated as a percentage of all readings on a given day.

2.4 Statistical analyses

Connected pen and CGM data were aggregated to a single value for both adherence level and TIR for each participant on each day. Subsequently, a weekly mean TIR and mean adherence were computed for each participant. For the first adherence metric, dose deviation, the weekly adherence was calculated as a mean of the seven days, while weekly adherence for the second and third adherence metrics, dose deviation ≤20%, and the traditional metric, was calculated as the percentage of the seven days where the adherence level was ≤20% or 100%, respectively. Finally, an overall weekly mean TIR and mean adherence (all three metrics) were determined by calculating the mean across all participants.

To test the strength of the linear relationship between TIR (dependent variable) and adherence (independent variable), the coefficient of determination (r^2) based on univariate linear regression analysis was calculated for each adherence metric. A significance level of $p < 0.05$ with Bonferroni correction was predefined for all statistical comparisons.

All data analyses were performed using Python 3.7 and relevant packages (Pandas version 1.4.4, Numpy version 1.19.5, Matplotlib version 3.5.2, and Scikitlearn version 1.0.2).

3. Results

3.1 Participant characteristics

Overall, data from 106 participants were included in this analysis. A summary of participant characteristics is shown in Table 1.

Table 1. Participant characteristics at baseline.

Characteristic	**N = 106**
Age (years)	61.9 ± 10.2
Female	44 (41.5%)
Body mass index (kg/m^2)	33.7 ± 6.2
HbA1c (mmol/mol)	64.2 ± 14.5
Diabetes duration (years)	19.7 ± 13.9
Insulin treatment	
Basal only	57 (53.8%)
Basal-bolus	49 (46.2%)
Mix insulin	0 (0%)
Daily insulin use (IU)[a]	69.8 ± 54.1
Type of basal insulin	
Human insulin	5 (4.7%)
Insulin detemir	1 (<1%)
Insulin glargine U100	55 (51.9%)
Insulin glargine U300	17 (16.0%)
Insulin degludec	28 (26.4%)
Other anti-diabetic medications	3.3 ± 1.0
Metformin	74 (69.8%)
Sulfonylurea	1 (0.9%)
DDP-4	5 (4.7%)
GLP-1	66 (62.3%)
SGLT2	46 (43.4%)
Number of diabetes complications[b]	1.3 ± 1.3
Retinopathy	25 (23.6%)
Nephropathy	37 (34.9%)
Neuropathy (with pain)	23 (21.7%)
Neuropathy (without pain)	22 (20.8%)
Diabetic foot ulcer (previous)	5 (4.7%)
Diabetic foot ulcer (present)	4 (3.8%)
Macroangiopathy	21 (19.8%)
Severe hypoglycemia in the last 12 months (yes)	5 (4.7%)
Comorbidities[c]	2.7 ± 0.9
Hypertension	86 (81.1%)
Cardiovascular disease[d]	30 (28.3%)
Overweight	90 (84.9%)
Hyperlipidemia	82 (77.4%)
Systolic blood pressure (mmHg)	139.7 ± 16.4
Diastolic blood pressure (mmHg)	81.4 ± 10.4
Weekly alcohol consumption	
0-5 units	92 (86.8%)
6-10 units	5 (4.7%)
11-15 units	7 (6.6%)
16-20 units	2 (1.9%)
>20 units	0 (0%)
Smoking status	
Yes	11 (10.4%)
No, but previously	52 (49.1%)
No	43 (40.1%)
Relationship status	
Lives alone	29 (27.4%)
Cohabitant	77 (72.6%)
Education	
No education	0 (0%)
Primary or secondary school	14 (13.2%)
High school	8 (7.5%)
Vocational education	30 (28.3%)
Medium tertiary education	43 (40.6%)
Long tertiary education	11 (10.4%)
Exercise per week (hours)[e]	

0-5	72 (67.9%)
6-10	28 (26.4%)
11-15	4 (3.8%)
16-20	0 (0%)
>20	2 (1.9%)

Continuous variables are presented by mean ± standard deviation (SD) and categorical variables by number (percentage).
[a] Total daily insulin use including both basal insulin and contingent bolus insulin use.
[b] Out of a total of seven listed complications.
[c] Out of a total of four listed comorbidities.
[d] Cardiovascular disease refers to all cardiovascular diseases
[e] Includes e.g., walking, and cycling to/from work

3.2 Raw adherence and TIR data

A positive, approximately linear relationship between adherence and TIR was observed in the raw data, see Figure 2. Notably, TIR decreases when adherence drops below 70%, but when adherence exceeds 70%, there is no corresponding increase in TIR. However, there was considerable variability between the minimum and maximum values within each bin.

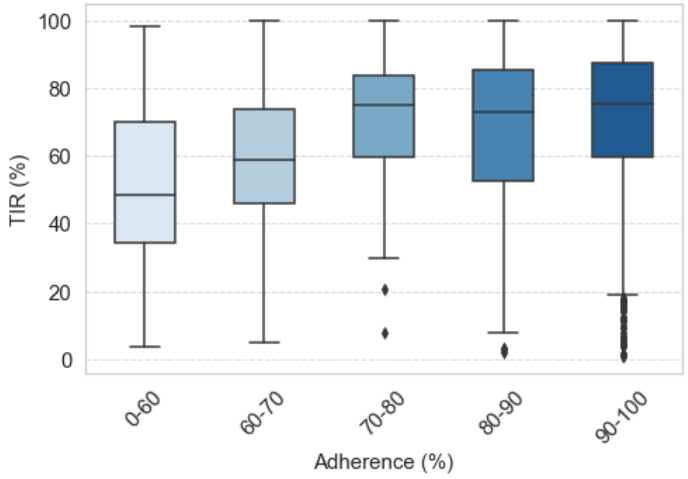

Figure 2. Boxplots illustrating the distribution of TIR across binned adherence levels using the raw data. Data comprises average weekly values for adherence level and TIR for each participant (106 participants x 11 weeks = 1166 pairs of daily basal dose adherence and TIR). Adherence levels are binned (0-60%; 60-70%; 70-80%; 80-90%; 90-100%).

3.3 Adherence levels

Quantification of adherence through the different adherence metrics yields distinct adherence levels. Participants demonstrated high adherence levels when quantified as dose deviation (92.4% ± 16.8%) and the dose deviation ≤20% (91.9% ± 17.9%), respectively. In contrast, the participants were only considered moderately adherent

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(74.0% ± 31.9%) when employing the traditional metric. Figure 3 presents the mean TIR and adherence level across all participants for each week during the trial.

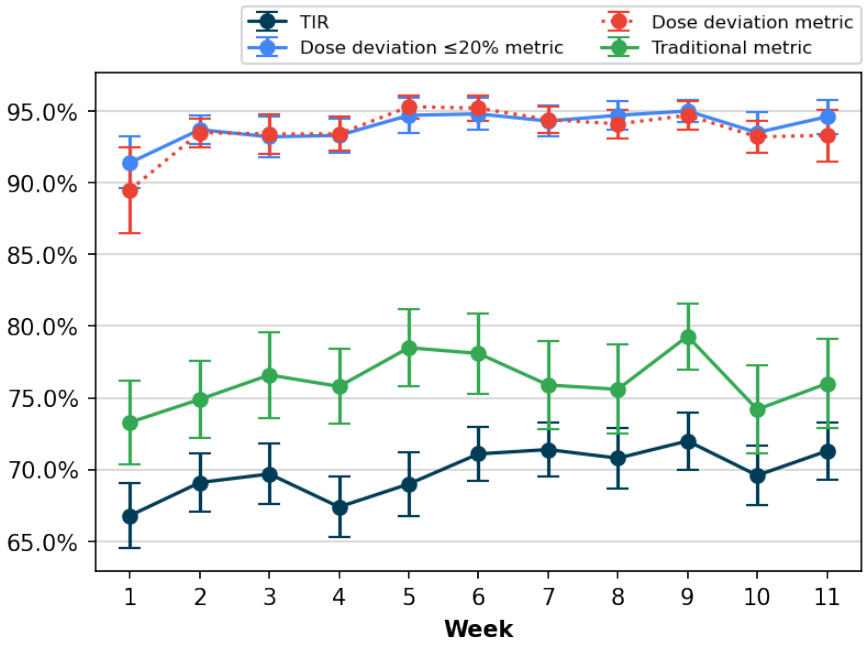

Figure 3. Weekly mean TIR and adherence level (in percentage) and standard error of the mean, SEM. Adherence was calculated using dose deviation, dose deviation ≤20%, and the traditional metric.

3.4 Relationship between adherence metrics and TIR

The univariate linear regression unveiled a distinct relationship between TIR and adherence level, see Table 2 and Figure 4.

Table 2. Results from the univariate linear regression, showing the 95% confidence interval (CI) of the linear slope.

Adherence metric	R^2	95% CI	P-value
Dose deviation	0.43	0.09, 1.30	0.08
Dose deviation ≤20%	0.67	0.61, 2.00	0.006
The traditional metric	0.35	-0.02, 1.04	0.23

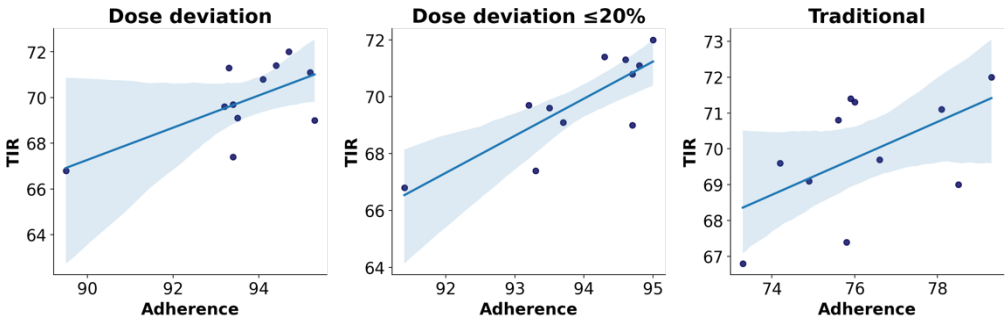

Figure 4. Scatterplots for the dose deviation metric and TIR, the dose deviation ≤20% metric and TIR, and the traditional metric and TIR.

A robust and statistically significant linear relationship (R^2 = 0.67, 95% CI [0.61, 2.00], p = 0.006) was observed between TIR and adherence, with adherence quantified as dose deviation ≤20%. In contrast, while adherence quantified as dose deviation also demonstrated a relationship with TIR, it was comparatively weaker (R^2 = 0.43, 95% CI [0.09, 1.30], p = 0.08). Adherence quantified by the traditional metric showed the weakest relationship (R^2 = 0.35, 95% CI [-0.02, 1.04], p = 0.23) with TIR. Notably, both the relationship between the traditional metric and the dose deviation metric were found to be statistically non-significant.

4. Discussion

This study evaluates the relationship between adherence to basal insulin therapy and TIR in people with T2D. Our findings reveal a significant linear and positive relationship between basal insulin adherence and glycemic control evaluated by TIR. This suggests that greater adherence to basal insulin therapy is associated with improved TIR. A notable decrease in TIR was observed when adherence fell below 70%. However, once adherence surpassed this threshold, further increases did not lead to further improvements in TIR. Furthermore, we observed a variability between the minimum and maximum values for adherence and TIR. This variability suggests individual differences in TIR. The observed relationship between adherence and TIR underscores the importance of adherence in the management of T2D, but these findings warrant further research to better understand the mechanisms driving this relationship [13].

While previous research [15] has established a link between adherence and glycemic outcomes in people with T1D, our study provides evidence of this relationship in people with T2D. This is significant given the differences in disease pathophysiology and treatment approaches between T1D and T2D [5]. Moreover, our findings highlight the importance of considering adherence to basal insulin therapy as a determinant of glycemic control in people with insulin-treated T2D, emphasizing the need for interventions aimed at improving adherence in this population.

Our results revealed a strong linear relationship between TIR and adherence when adherence was quantified using the dose deviation ≤20% metric. Conversely, a weaker and statistically non-significant relationship was found when dose deviation was applied as the adherence metric. This may be attributed to the exclusion of certain variability in adherence data when applying the ≤20% threshold for dose deviation. This suggests that the extent of deviation from the recommended basal insulin dose directly influences glycemic control; larger deviations and missed doses have more impact on glycemic control than smaller deviations. In line with our findings, Danne et al. (2024) demonstrated that missed basal doses are associated with a reduction in TIR. However, their study utilized a different method of quantifying adherence. They focused solely on missed doses, defining a missed basal insulin dose as one where more than 40 hours elapsed between two doses. In contrast, our study extends this approach by incorporating dose deviations into the adherence metric. This addition provides further nuance, indicating that both the frequency of missed doses and the degree of dose deviation contribute to TIR.

It should be noted that the traditional metric employed in our study is different from the commonly used standard adherence measures. Our traditional metric is based on data from both CGM and connected insulin pens, whereas the standard adherence measures rely on self-reported data and/or pharmacy claims-based calculations. However, both our traditional metric and the standard measures only account for whether insulin was administered correctly compared to the recommended dosage and do not [19] consider the dosage magnitude [19]. Therefore, we believe that our traditional metric is comparable to the standard adherence measures.

Participants in our study demonstrated notably high adherence levels compared to prior findings [24–26]. This may be explained by the potential influence of continuous glucose monitoring (CGM) and the close telemonitoring of participants throughout the DiaMonT trial [21]. By having immediate access to blood glucose levels, individuals

could be empowered to make informed decisions regarding basal insulin administration and thus promptly respond to fluctuations in blood glucose levels.

A key strength of our study was the use of data from connected insulin pens enabling the collection of accurate injection information. Nonetheless, certain limitations should be considered when interpreting the results. Our analysis did not include or adjust for factors such as the concurrent use of other anti-diabetic medications [5], including bolus insulin, the influence of CGM [27], weight, and residual beta cell function (endogenous insulin production) [28]. Additionally, our results indicate that when adherence level exceeds 70% other factors, besides adherence level, may influence TIR. While recognizing the potential effects of these factors on glycemic control, we deliberately opted for a simplified analysis, given the novelty of our study. Future research should encompass multiple regression analyses including various factors to determine the relationship further. Furthermore, despite approximately three months of data being collected per participant, we confined our analysis to 1 to 11 weeks of the trial. This decision partly stemmed from applying a forward shift of +3 days to the adherence level data leading to days with no adherence data in week 0 and partly from the observation of >25 % missing CGM data in week 12.

5. Conclusions

Our study demonstrated a significant relationship between adherence to basal insulin therapy and glycemic control as evaluated by TIR in people with insulin-treated T2D. These findings underscore the importance of basal insulin adherence in achieving optimal glycemic outcomes and highlight the potential utility of TIR as a clinical marker for monitoring glycemic control in this population. The magnitude of deviation from the recommended basal insulin dose seems to influence glycemic control and an adherence measure including the dose deviation may offer a more robust measure of adherence than standard adherence measures commonly used in research and clinics today.

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