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Characterizing insulin dosing behaviour and glycaemic excursions: Development of metrics using connected insulin pen and continuous glucose monitoring

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Abstract

Aims: Connected insulin pens (CIPs) provide insulin dosing data that can be leveraged to drive improvements in glycaemic control. To realize this potential in routine care, insulin data need to be distilled into actionable insights for clinicians. We describe two algorithms for detecting glucose excursions using continuous glucose monitoring (CGM) data and then link excursions to CIP data to derive "insulin metrics" characterizing suboptimal bolus dosing practices.

Materials and Methods: This post hoc analysis used CGM and CIP data from a 12-week observational study (clinicaltrials.gov: NCT03368807) of 64 adults with type 1 or type 2 diabetes receiving multiple daily injection insulin therapy and glycated haemoglobin ≥8%. Two updated algorithms were applied to analyse glucose excursions associated with pre-meal boluses, missed bolus doses (MBDs), delayed boluses and correction boluses.

Results: Glycaemic metrics obtained using both algorithms were similar. Time in range (%TIR) was lower, and time above range (%TAR) and glycaemic variability (%GV) were higher, on days with MBDs. Compared with pre-meal boluses, delayed and correction boluses were followed by glucose excursions with larger change in glucose, longer duration with glucose >180 mg/dL, lower post-excursion %TIR and higher post-excursion %TAR; excursions following MBDs showed lower %TIR, higher %TAR and lower percent recovery. Glucose excursions were larger and longer when CGM was masked than when unmasked.

Conclusions: This analysis demonstrates "insulin metrics"—characterizations of insulin dosing behaviour derived from integrated CGM and CIP data—and provides a foundation for future work that will expand the understanding of an individual's insulin self-administration practices and improve clinical decision-making.

KEYWORDS
continuous glucose monitoring (CGM), glycaemic control, hypoglycaemia, insulin therapy, observational study

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1 | INTRODUCTION

Despite advances in glucose measurement technology and improved insulins, about 50% of people with diabetes using insulin therapy fail to reach recommended glycaemic goals.[1] The reasons for failure to meet glycaemic goals are multifactorial but include the complexity of insulin regimens and the suboptimal use of bolus insulin for anticipated food intake and to correct hyperglycaemia. Approximately 20% to 65% of people with diabetes report missed bolus doses (MBDs) of insulin,[2–4] and higher rates of missed or delayed bolus doses are associated with inadequate glycaemic control.[2,4]

Metrics derived from continuous glucose monitoring (CGM) are increasingly being used in conjunction with the traditional measures of glycaemic control, mainly glycated haemoglobin (HbA1c), in the real-world management of diabetes.[5] Connected insulin pens (CIPs) can be useful tools to identify suboptimal insulin dosing practices and facilitate optimization of insulin injection therapy.[6–9] The introduction of standardized glucose and insulin data reports for people on multiple daily injections using CIP and CGM will be an important step to support the use of CIP in diabetes care delivery.[10] To realize this potential in routine care, there is a need for insulin data to be distilled into actionable insights that can guide clinical decision-making and for standardization of terminology and metrics,[10,11] similar to progressive standardization for CGM metrics.[12–14]

In this report, we describe the development of two algorithms designed to detect food-related glucose excursions using CGM data from a previously described observational study.[15] We then linked these excursions to insulin bolus timing from CIP data to characterize insulin dosing practices and glucose profiles associated with different types of dosing patterns, that is, pre-meal boluses, MBDs, delayed boluses and correction boluses.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a post hoc, retrospective analysis of data from a previously described, 12-week, 2-period, multicentre, single-arm observational study conducted in the United States (ClinicalTrials.gov identifier: NCT03368807).[15] The evaluable study population included 64 adults with type 1 diabetes (T1D; $n = 38$) or type 2 diabetes (T2D; $n = 26$) who were using ≥3 doses of bolus insulin (<40 U) per day at screening and documented HbA1c ≥8% during the previous 6 months.[15] At baseline, mean (standard deviation, SD) age was 47.7 (11.9) years, and mean (SD) HbA1c was 9.6% (1.8%); participants had a mean (SD) 19.8 (10.4) years diabetes duration.[15] Baseline CGM mean (SD) of TAR, TIR and TBR were 49.8% (19.0%), 46.4% (17.1%) and 3.8% (3.8%), respectively. Prior to enrolment, participants had received insulin lispro U-100 (54.7%), insulin aspart (43.8%) or insulin glulisine (1.6%).[15] During the study, participants used an investigational CIP (Eli Lilly and Company, Indianapolis, IN) to inject insulin lispro U-100; the insulin dose and timing data were captured by the CIP. Participants also used a commercial CGM device (Dexcom G5®, DexCom Inc., San Diego, CA) to measure interstitial fluid glucose, which was standardized with consistent threshold settings, ensuring uniform detection of glucose excursions. Participants were masked to CGM data during Weeks 1 to 6 (period 1) and unmasked during Weeks 7 to 12 (period 2). CGM alarms were not used during the first 8 weeks. At Week 9, alarms were activated and adjusted per the discretion of the study clinician. The study did not collect data on meal timing or composition. The study team preferred to avoid creating any artificial alteration in participant food choices or dosing behaviour, and this outweighed the value that these data could have added to the analysis. Further details are available in the primary study publication.[15]

The study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by ethics review boards at each of the six study sites. All participants provided written informed consent before any study procedures were undertaken.

2.2 | Identification of glucose excursions

We developed two methods, designated modified mean amplitude of glucose excursion+ (MAGE+) and Delta G, to identify glucose excursions from CGM data (Supplementary Appendix).

The modified MAGE+ method was adapted from the original MAGE metric of Service et al.[16] and the CGM-based MAGE algorithm of Baghurst[17] but utilizes only upward excursions (i.e., increases in glucose). In brief, sensor glucose data were first smoothed using a symmetrical, 9-point, exponential moving average with decreasing weights to smooth the data, replacing the first and last four glucose values with their arithmetic average. Smoothing was conducted to mitigate noise and reduce the likelihood of false-positive excursion detections. Local maxima and minima were identified in the smoothed data to identify candidate nadir-peak pairs, and the difference in glucose (ΔG) for each pair was calculated. Only those pairs with a glucose increase ≥70 mg/dL were retained, then stored and displayed as significant excursions.

The Delta G method was based in part on a method presented at the American Diabetes Association Scientific Sessions by Norlander et al.[18,19] In brief, all hypoglycaemic events (sensor glucose <70 mg/dL) were identified, excluding those lasting <15 min; if the duration was ≥15 min, the algorithm temporarily halted excursion detection during hypoglycaemia then reset the starting point of an excursion following hypoglycaemia recovery. A 2-h moving window was then used to identify glucose excursions with glucose increases ≥70 mg/dL in which both the onset and peak of the excursion occurred within a single 2-h window. Each peak within the window was saved for further analysis. If hypoglycaemia occurred between the onset and peak of a candidate glucose excursion, the excursion was excluded. Adjacent nadir-peak pairs that were separated by <20 min were merged to exclude pairs that crossed hypoglycaemia periods. Each excursion "event" typically included multiple individual data points within a candidate start-time range and others within a plausible end-time range; all possible combinations of plausible start and end data points were evaluated, aiming to identify suitable excursions that were

characterized by a balance of achieving the highest glucose peak amplitude at the endpoint, reaching the lowest range at the starting point and maintaining a high rate of change (ROC) from start to finish. Equal weights were assigned to the nadir, peak, and ROC to select the excursion pair. Excursion pairs with ≤2 h between them were merged using strict criteria that cover special "edge" cases, specifically, (1) the nadir at the onset of the second excursion was higher than the peak of the first excursion, (2) there were <3 consecutive glucose readings lower than the peak of the first excursion and (3) all readings between the excursions were >180 mg/dL, ensuring consistency in continuous excursions.

For both the "modified MAGE+" and "Delta G" methods, the glucose level at the onset of the excursion (G_0) was required to be ≥70 mg/dL to reduce the likelihood that excursions were due to over-treatment/rebound from a hypoglycaemic episode. The excursion peak (G_{max}) was required to be >180 mg/dL, and an arbitrary, preselected glucose increment (ΔG) of ≥70 mg/dL above baseline glucose (G_0) was required. MBDs were identified using both methods and were defined as no insulin bolus administration occurring between 2 h before and 4 h after the onset of a glucose excursion. The 2-h window was chosen to allow a sufficient number of episodes to be analysed, to support the identification of behavioural patterns that may need improvement. The 4-h missed bolus period serves as a maximum window where, if the ROC falls below the threshold of <1 mg/min, the algorithm terminates the window before the 4-h limit. This timeframe was chosen as it generally covers the primary glucose rise associated with a meal, capturing the most significant period for assessing suboptimal bolusing behaviours. The 4-h window also limits the number of detected glucose excursions, allowing maintained focus on repeated patterns, which could otherwise be diluted with shorter intervals.

Glycaemic metrics were analysed for both methods (defined in Table 1) and included means and SDs for glucose concentration, time in range (%TIR), time above range (%TAR), time below range (%TBR) and coefficient of variation (%CV). Glycaemic metrics were analysed separately for days with ≥1 MBD and days without MBDs separately for the masked and unmasked periods. Data from participants with T1D and T2D were combined for analysis. Comparisons between days with and days without MBDs were made within each participant using paired *t*-tests for both masked and unmasked periods.

TABLE 1 Definitions and parameters used in data analysis.

Parameter	Definition
G_0	Initial blood glucose value at time of onset of the glucose excursion
G_{max}	Maximal glucose value achieved during upstroke and declared to be the maximum glucose value achieved during the excursion
ΔG	Amplitude of a glucose excursion: $G_{max} - G_0$
T_{max}	Time when G_{max} is achieved, following onset of a glucose excursion
% Recovery	Percentage of return of glucose value from observed G_{max} towards G_0 at any specified time (t) after T_{max}: $\%Recovery = 100 \times (G_{max} - G_t)/(G_{max} - G_0)$
% TIR	Percentage of time that glucose is in the ≥70 to 180 mg/dL range during the 6 h after onset of a glucose excursion (or until the onset of the next glucose excursion)
% TAR	Percentage of time that glucose is >180 mg/dL during the 6 h after onset of a glucose excursion (or until the onset of the next glucose excursion)
% TBR	Percentage of time that glucose is <70 mg/dL during the 6 h after onset of a glucose excursion (or until the onset of the next glucose excursion)

Abbreviations: TAR, time above range; TBR, time below range; TIR, time in range.

2.3 | Definition of bolus types

We then used the CIP data together with CGM data to examine four types of bolus dose associated with glucose excursions identified by the Delta G method, as follows (Table 2):

- Pre-meal bolus–dose injection occurs within 2 h before the onset of a glucose excursion; the ROC of sensor glucose must be <1 mg/dL/min during the 20 min before the injection, indicating a stable pre-injection glucose level.
- Delayed bolus–dose injection occurs within 4 h after the onset of a glucose excursion but before the apex of the upstroke is achieved; the ROC of sensor glucose must be ≥1 mg/dL/min during the 20 min before the injection, indicating a rapid pre-injection increase in glucose level.
- MBDs (as defined above)—no recorded dose injection occurs between 2 h before the onset and 4 h after the onset of a glucose excursion.
- Correction bolus—dose injection occurs up to 4 h after the onset of a glucose excursion, whether or not there had been a previous bolus dose.

The following parameters (defined in Table 1) were analysed for each type of bolus: number of glucose excursions associated with each type of bolus; G_0; G_{max}; ΔG; time from onset of the excursion to maximum glucose (T_{max}); duration with glucose >180 mg/dL; percentage of excursions that fell below 120 mg/dL within 6 h after the onset of the excursion (and before the start of the next excursion); percentage recovery from maximum glucose (G_{max}) towards baseline (G_0) within 6 h; and %TIR and %TAR within 6 h after the start of glycaemic excursions. All data (including T1D and T2D, masked and unmasked periods) were combined for analysis. Glycaemic parameters for delayed, missed and correction boluses were compared with those for pre-meal boluses using a Wilcoxon rank sum test.

2.4 | Glucose excursion profiles

The average shape of the glucose excursion profile was calculated for each bolus type identified using the Delta G method, separately

TABLE 2 Criteria to characterize glucose excursions and associated insulin boluses based on timing of insulin bolus relative to onset of excursion.

Bolus type	Time from insulin injection to onset of detectable excursion (minimum to maximum, hours)	Criteria	
		Bolus time	Rate of change in sensor glucose within past 20 min
Pre-meal	−2 to 0	Bolus within 2 h before onset of excursion	<1 mg/dL/min
Delayed	0 to 4	Bolus after onset of excursion	≥1 mg/dL/min
Missed	−2 to 4	No recorded bolus between 2 h before onset of excursion to 4 h after onset of excursion	NA
Correction	0 to 4	Bolus after peak of the excursion and up to 4 h after the onset of excursion	NA

Abbreviation: NA, not applicable.

for the masked and unmasked periods in participants with T1D and T2D. The time of onset of each excursion was defined as $t = 0$, and median glucose values were calculated as a function of time from $t = 0$ to $t = 6$ h. We applied weighted least-square regression with natural cubic splines to model the trend of glucose excursions in the 6 h after the nadir, where the weights for each glucose excursion were set to account for differing numbers of observations at different time points.[20] To be more specific, we considered the following additive model for glucose change after the onset of each excursion:

$$\Delta G(t) = \Delta G_0(t) + \sum_{j=1}^{p} x_j \beta_j(t) + \epsilon$$

where $\Delta G(t)$ is the response variable representing the glucose change at time t from the nadir, $\Delta G_0(t)$ and $\beta_j(t)$ are the baseline-adjusted glucose change and the time-varying coefficient for covariate x_j at time t from the nadir, respectively, and ϵ is the random error term with expectation zero. We adopted the nonnegative natural cubic spline basis functions introduced in Wang and Yan[20] and utilized the R package "splines2"[21] for their implementations. We applied the same set of natural spline basis functions to model the baseline glucose change and time-varying coefficients for simplicity. The boundary knots were placed at the onset and at 6 h later, and internal knots were placed at 1.5, 3.0 and 4.5 h after onset. We incorporated a constraint that the glucose change should start from zero.

All statistical analyses were conducted using the R statistical package (https://www.r-project.org/).

3 | RESULTS

3.1 | Glycaemic metrics on days with or without MBDs

Glycaemic metrics were generally similar when analysed by either the modified MAGE+ or Delta G methods (Table 3). Overall, at least one MBD occurred on a mean of 15.9 to 16.8 days in each 21-day segment during both masked and unmasked CGM periods, with an average of 1.3 to 1.5 MBDs per day. The high number of MBDs per day and frequent days with MBDs are consistent with the poor glycaemic control and high HbA1c that was observed and expected in this study population.[15]

%TAR: With both methods, %TAR was significantly higher on days with MBDs than on days without MBDs during the period with masked CGM. In contrast, there was no significant difference between days with and without MBDs during the period when CGM was unmasked (Table 3).

%TBR: The %TBR was significantly lower on days with MBDs than on days without MBDs during both masked and unmasked periods when analysed by the modified MAGE+ method but not when analysed by the Delta G method (Table 3).

%CV: During the unmasked period, glycemic variability as measured by %CV was significantly lower on days without MBDs than on days with MBDs when using both methods of analysis. However, during the masked period, %CV was statistically significantly lower on days without MBDs when analysed by Delta G but not when analysed by modified MAGE+ (Table 3).

3.2 | Characterization of glucose excursions for different bolus types

A total of 350 754 candidate glucose excursions were identified from CGM data by the Delta G method, pooling data from both the masked and unmasked periods (Table 4). Of these excursions, 23% were accompanied by a pre-meal bolus and 19% by a delayed bolus; 34% were not associated with administration of bolus insulin (i.e., represented a "missed bolus"). Some glucose excursions were accompanied by boluses meeting criteria for both delayed and correction boluses, and approximately 39% of boluses were classified as correction boluses. Glucose excursions associated with pre-meal boluses were characterized by significantly higher %TIR and lower %TAR during the 6 h following the onset of the excursion than glucose excursions associated with delayed or MBDs (Table 4). Glucose excursions associated with MBDs recovered more slowly towards

TABLE 3 Glycaemic metrics for days with ≥1 missed bolus dose versus days without missed bolus doses in the masked CGM and unmasked CGM periods assessed by the modified MAGE+ and Delta G methods ($N = 64$ participants).

	Modified MAGE+				Delta G			
Metric	Masked CGM period		Unmasked CGM period		Masked CGM period		Unmasked CGM period	
Days with ≥1 MBD per 21-day segment	16.1 ± 4.3		15.9 ± 3.9		16.8 ± 4.7		16.8 ± 3.6	
MBD/day	1.3 ± 0.5		1.4 ± 0.5		1.4 ± 0.5		1.5 ± 0.5	
	Days with MBD	Days without MBD	Days with MBD	Days without MBD	Days with MBD	Days without MBD	Days with MBD	Days without MBD
Glucose (mg/dL)	202 ± 45	189 ± 54	190 ± 40	179 ± 51	201 ± 46	188 ± 59	189 ± 41	184 ± 51
TIR (%)	42 ± 18	45 ± 23	50 ± 20	51 ± 25	43 ± 19	48 ± 26	49 ± 19	53 ± 25
TAR (%)	54 ± 20	47 ± 25**	48 ± 21	44 ± 27	53 ± 21	47 ± 28*	48 ± 21	45 ± 27
TBR (%)	3.5 ± 3.9	8.1 ± 8.6**	2.3 ± 2.7	4.9 ± 5.9**	4.2 ± 4.7	5.2 ± 7.6	2.9 ± 3.9	2.1 ± 4.4
CV (%)	38 ± 8	41 ± 14	36 ± 6	33 ± 11**	39 ± 8	35 ± 12**	36 ± 6	31 ± 10**

Note: Data are mean ± SD. Comparisons were made within each participant using paired *t*-test (MBD days vs. non-MBD days) for both masked and unmasked periods.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; MAGE, mean amplitude of glycaemic excursion; MBD, missed bolus dose; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range.
*$p < 0.05$; **$p < 0.01$.

TABLE 4 Glucose excursions following different types of insulin boluses assessed by the Delta G method ($N = 64$ participants; masked and unmasked periods combined).

Parameter	Pre-meal bolus	Delayed bolus	Missed bolus	Correction bolus
Number of candidate excursions[a] (total = 350 754)	81 799	67 550	117 681	137 727
G_0 (mg/dL)	153.9 ± 39.3	160.1 ± 42.5	153.2 ± 36.8	157.1 ± 5.6
G_{max} (mg/dL)	245.1 ± 47.2	269.7 ± 52.5	245.3 ± 44.9	261.3 ± 72.7
ΔG (mg/dL)	92.1 ± 25.2	109.6 ± 29.6**	92.0 ± 19.8	99.7 ± 19.7
T_{max} (min)	91.0 ± 21.6	93.2 ± 12.3	95.0 ± 10.6	95.9 ± 10.3
Duration with glucose >180 mg/dL (h)	1.19 ± 0.71	1.52 ± 0.94*	1.24 ± 1.03	2.82 ± 1.20*
% Excursions falling to <120 mg/dL within 6 h[b]	36.7 ± 33.0	28.1 ± 30.3	19.2 ± 17.9*	27.0 ± 23.5
% Recovery towards baseline within 6 h[b]	98.1 ± 73.5	91.0 ± 65.4	64.1 ± 35.7**	86.3 ± 27.5
% TIR within the 6 h following onset of excursion[b]	45.2 ± 24.2	34.5 ± 22.0**	36.7 ± 21.0*	32.5 ± 20.4**
% TAR within the 6 h following onset of excursion[b]	53.3 ± 25.2	64.1 ± 23.1**	62.7 ± 21.3*	66.2 ± 21.4**

Note: Data are mean ± SD, except where noted.
Abbreviations: SD, standard deviation; TAR, time above range; TIR, time in range.
[a]Some excursions were classified as more than one type of bolus.
[b]For 6 h following onset of excursion or until the start of the next excursion, whichever comes first.
*$p < 0.05$; **$p < 0.01$ compared with pre-meal bolus (Wilcoxon rank sum test).

baseline, with a significantly smaller percentage recovery and a smaller percentage of excursions falling below 120 mg/dL within 6 h compared with pre-meal boluses. Glucose excursions with an accompanying correction bolus were characterized by a considerably longer duration with glucose >180 mg/dL and lower percentage recovery. Following grouping, the total number of representative excursions was 10 780 across the 64 participants over the 12-week period, averaging approximately 2 identified excursions per participant per day. Of these excursions, 19.5% were accompanied by a correction bolus, 15.8% by a delayed bolus and 12.2% by a pre-meal bolus; 52.5% were not associated with bolus insulin administration (i.e., represented a "missed bolus").

3.3 | Glucose excursion profiles during masked and unmasked CGM periods

To further characterize glucose excursions associated with the four categories of insulin boluses, we assessed glucose excursion profiles for each type of bolus during the masked and unmasked CGM periods for both T1D and T2D (Figure 1). In total, we analysed 5663 glucose excursions (29 230 h of CGM data from up to 6 h following the onset of each excursion) from all 64 participants over an average period of 38 days. Overall, the patterns for glucose excursion profiles for each of the four categories of bolus were similar in T1D and T2D, except that excursion amplitude was higher and recovery time was longer in

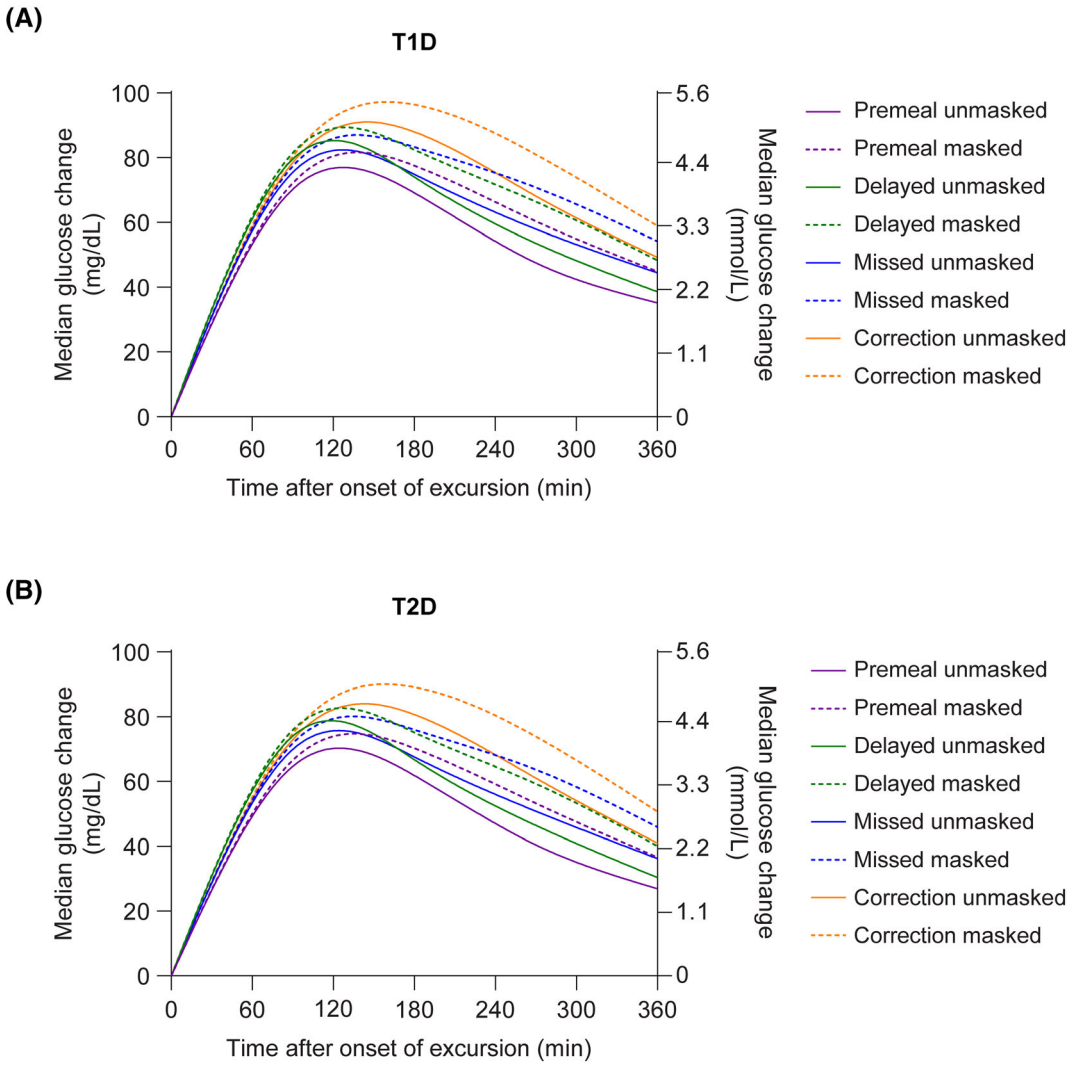

FIGURE 1 Glucose excursion profiles for different insulin bolus dose types during the masked and unmasked CGM periods in participants with (A) T1D and (B) T2D. CGM, continuous glucose monitoring; T1D, type 1 diabetes; T2D, type 2 diabetes.

T1D than in T2D. Regardless of type of diabetes and type of bolus, glucose excursions were slightly higher and more prolonged when the CGM was masked than when it was unmasked. As expected, the amplitude and duration of excursions associated with pre-meal boluses were smaller than for the other three categories of bolus.

4 | DISCUSSION

The combination of CGM and CIP data can provide a more comprehensive understanding of the impact of an individual's insulin self-administration practices on glycaemic control. However, to transform the abundant data from these devices into actionable insights, analytical approaches to identify clinically important suboptimal dosing practices are needed. In this study, we investigated two methods for characterizing glucose excursions using CGM data and evaluated the integration of CIP-generated bolus data to derive metrics characterizing suboptimal insulin dosing practices, such as missed and delayed bolus doses.

Both the modified MAGE+ and Delta G methods to identify glucose excursions produced similar but not identical results in the analysis of glycaemic metrics, suggesting that either method may form the basis of future, clinically applicable algorithms. Although the current exploratory analysis does not allow us to draw definitive conclusions regarding the relative merits of each algorithm, our results support continued refinement and testing of automated methods to detect and analyse food-related glucose excursions using CGM data. Regardless of the algorithm used, %TAR and %CV were generally higher and %TBR was lower on days where at least one insulin bolus dose was missed, although the differences were not always statistically significant. This observation is consistent with previous findings by ourselves[15] and multiple others[2–4] that MBDs are associated with poorer glycaemic control. The identical setting of key excursion parameters, such as a minimum nadir (G_0) of 70 mg/dL and a minimum amplitude (ΔG) of 70 mg/dL, was very likely a major factor contributing to the similarity of results obtained with the two methods. Although we also explored a wide range of possible values for the parameters G_0 and

ΔG (data not shown), these parameters may need further optimization and may need to be customized for individual studies. Further refinement of either or both methods is required, as is a rigorous assessment of their respective strengths and weaknesses.

MBDs, delayed bolus doses and other types of suboptimal insulin doses are known to contribute to poor glycaemic control.[2–4] In this study, we characterized glycaemic metrics and excursion profiles of MBDs, delayed boluses and correction boluses and compared these with appropriately timed pre-meal boluses. As previously noted,[15] glycaemic control improved during the unmasked CGM period compared with the masked period, reaffirming the benefit of real-time CGM. All three types of suboptimal boluses were generally accompanied by larger and longer-lasting glucose excursions, as well as higher %TAR and lower %TIR during the 6-h post-excursion period, compared with pre-meal boluses. However, glucose excursions related to different bolus types exhibited some distinct features, such as delayed boluses resulting in particularly high ΔG and correction boluses being associated with prolonged excursions and slower return to baseline. Moreover, glucose excursion profiles reached a lower maximum glucose level and recovered more quickly during the unmasked CGM period than during the masked period, regardless of bolus type or diabetes type. These findings are consistent with the overall better glycaemic control with unmasked CGM observed here and in the primary analysis of this study,[15] reaffirming the benefit of real-time CGM and hypo- and hyperglycaemic alarms.

Glucose excursions that occurred after MBDs were not substantially larger than those associated with a pre-meal bolus. Several factors may contribute to this observation. For example, the requirement for ΔG to be ≥70 mg/dL may have excluded smaller excursions resulting from meals with more-than-adequate pre-meal bolus doses. Additionally, MBDs may occur in the context of small meals or snacks, which the person does not regard as requiring insulin injection, whereas pre-meal boluses may be given ahead of larger, planned meals. Finally, our analytical approach and the potential insights derived from the data are limited by the absence of meal information.

The methods to detect and analyse glucose excursions developed and examined in this study, as well as the criteria to define MBDs and other suboptimal boluses, are expected to require further optimization and validation. Although both participants with T1D and those with T2D were included, the study was deliberately designed to recruit a patient population with poor glycaemic control (HbA1c >8.0%) and population-specific analyses have previously been reported;[15] validation in a population with better glycaemic control will be needed.

5 | CONCLUSIONS

This analysis shows that passively collected data from CIP and CGM devices, without any additional contextual data such as food intake or knowledge of the prescribed insulin dosing regimen, can provide actionable insights about insulin dosing behaviour. The widespread use of CGM has propelled the use of CGM metrics in the real-world management of diabetes.[5] As use of CIP increases, diabetes management could be further enhanced by the incorporation of insulin metrics—characterizing insulin dosing practices that contribute to suboptimal glucose control—into data reports.

AUTHOR CONTRIBUTIONS

HW contributed to conceptualization, writing–original draft, writing–review and editing. DR contributed to formal analysis, investigation, methodology, visualization, writing–original draft, writing–review and editing. JX contributed to conceptualization, data curation, formal analysis, methodology, software, visualization, writing–original draft, writing–review and editing. JJ contributed to investigation, visualization, writing–original draft, writing–review and editing. ED contributed to conceptualization, funding acquisition, investigation, resources, supervision, writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

HW was an employee of Eli Lilly and Company at the time the study was conducted. DR served as a consultant to Eli Lilly and Company during the course of this study. JX, JJ and ED are employees and stockholders of Eli Lilly and Company.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16249.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ROLE OF THE SPONSOR

Eli Lilly and Company was involved in the study design, data collection, data analysis and preparation of the manuscript.

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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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