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Rate of Change of Premeal Glucose Measured by Continuous Glucose Monitoring Predicts Postmeal Glycemic Excursions in Patients With Type 1 Diabetes: Implications for Therapy

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Abstract

Background: Patients with type 1 diabetes routinely utilize a single premeal fingerstick glucose to determine premeal insulin doses. Continuous glucose monitoring (CGM) provides much richer glycemic trend information, including glycemic slope (GS). How to incorporate this information into dosing decisions remains an open question.

Methods: We examined the relationship between premeal GS and postmeal glycemic excursions in 240 individuals with type 1 diabetes receiving CGM augmented insulin pump therapy. Over 23.5 million CGM values were synchronized with 264 500 meals. CGM values were integrated 2 hours premeal to compute GS and 2 hours postmeal to compute glycemic excursion outcomes. Postmeal hyperglycemia (integrated CGM glucose >180 mg/dL*hr) and postmeal hypoglycemic events (any CGM glucose < 70 mg/dL) were tabulated according to positive/negative premeal GS and according to GS bins commonly displayed as rate-of-change arrows on CGM devices.

Results: Positive versus negative premeal GS was associated with a 2.28-fold (95% CI 2.25-2.32) risk of postmeal hyperglycemia. Negative versus positive premeal GS was associated with a 2.36-fold (95% CI 2.25-2.43) increase in one or more postprandial hypoglycemic events. Premeal GS in the bin currently displayed as "no change" on existing CGM devices (–1 to 1 mg/dL/min), conferred a 1.82-fold (95% CI 1.79-1.86) risk of postprandial hyperglycemia when positive and a 2.06-fold (95% CI 1.99-2.15) increased risk of postprandial hypoglycemia when negative.

Conclusion: Premeal GS predicts postmeal glycemic excursions and may help inform insulin dosing decisions. Rate-of-change arrows on existing devices obscure clinically actionable glycemic trend information from CGM users.

Keywords

continuous glucose monitoring, glucose rate-of-change, insulin dosing, premeal glycemic trends, postprandial hyperglycemia, postprandial hypoglycemia

The standard clinical treatment of patients with type 1 diabetes and some patients with type 2 diabetes includes mealtime insulin doses that are determined by the anticipated carbohydrate intake and a single premeal blood glucose reading. This approach was devised when glycemic trend information was limited by the number of fingerstick glucose measurements it was practical to perform. Even if the recommended fingerstick tests before meals and snacks and at bedtime[1] are performed, most glycemic trends remain unobserved and therefore cannot be utilized for dosing decisions. Continuous glucose monitoring (CGM), by sampling interstitial glucose every 2 to 15 minutes depending on the specific device used, exponentially increases our knowledge of glycemic fluctuations without increasing the burden of fingerstick testing. Trials of CGM in individuals treated with basal-bolus insulin have shown promise in

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improving glycemic control without increasing hypoglycemia, but improvements over usual care with fingerstick monitoring have been modest (0.2-0.6% HbA1c) in controlled trials.[2,3,4]

There is a growing recognition of the need to maximize the clinical utility of CGM.[4] A deeper understanding of CGM-derived glycemic trends may enable more effective dosing algorithms, but the technology has out-paced the development of evidence-based recommendations. Many available CGM devices already display glycemic trend information such as glucose rate-of-change or glycemic slope (GS)[5] and surveys have shown that patients are incorporating this data into dosing decisions[6] in the absence of evidence or validated algorithms.

In order to provide empiric data that would guide the utilization of GS in insulin dosing decisions, we systematically examined the relationship between premeal GS and postmeal glycemic excursions from the STAR3 sensor-augmented pump therapy trial.[7] We quantified the relationship between premeal GS and postmeal glycemic excursions and examined the role of GS in predicting postmeal hyper- and hypoglycemia. In addition, we evaluated the usefulness of currently available GS data, provided in some devices as rate-of-change arrows, by examining the relationship between such premeal up/down arrows and subsequent, postmeal hyper- and hypoglycemia.

Methods

Subjects

Data were previously collected from subjects participating in the STAR-3 study of sensor-augmented pump therapy.[7,8] In brief, the subjects were ages 16 to 70 (mean age 42) and had type 1 diabetes of at least 2 years duration (mean 27 years), a glycated hemoglobin value of 5.8 to 10.0% (mean 7.2%), and had used insulin-pump therapy for more than 6 months. Subjects were followed and data collected over an average duration of 18 months. Subjects were instructed to dose insulin according to the "Bolus Wizard" which incorporated point glucose and carbohydrate counts, but did not specifically include CGM trend data.[7] Of the 247 enrolled subjects, 7 withdrew early and were excluded from analysis for lack of data. Subjects utilized the Paradigm Revel 2.0 insulin pump and Enlite glucose sensors (both Medtronic MiniMed, Northridge, CA). These sensors, which were used throughout the study, were calibrated with the study meter (Bayer Contour Next Link, Bayer HealthCare, Berlin, Germany) and have a previously established mean absolute relative difference between sensor and reference blood glucose values of 13.6%.[7] For each subject, data from the glucose sensor (with measurements every 5 minutes), calibration fingersticks, bolus wizard, and insulin pump were aggregated and harmonized according to time of input and administration.

Identification of "Meals," Premeal Glucose, and Glycemic Rate-of-Change

The timing of meals was established by identifying an insulin bolus that was within 10 minutes of a carbohydrate entry. The premeal blood glucose was established as the nearest single CGM glucose measurement occurring within 10 minutes of the bolus. CGM data from 2 hours prior to and 2 hours after the meal were extracted for each meal (n = 381 659 traces). Data traces were excluded (n = 117 159) if they had missing values or discontinuous jumps between adjacent CGM measurements (possibly caused by sensor malfunction or a user-driven recalibration). Premeal GS was calculated from 12 consecutive sensor values obtained in the 60 minutes prior to the bolus by linearly regressing the 12 sensor glucose values against time using a weighting function that prioritized sensor values starting 15 minutes prior to the bolus. The 15-minute prioritization scheme was selected to mimic the stated time-window of rate-of-change arrows on commercially available CGM devices.[9] Specifically the exponential weighting function used in the regression input was weight[i] = 0.4^i for i = sensor value 1 to 12.

Definition of Outcomes: Postmeal Glycemic Excursion, Hyperglycemia, and Hypoglycemia

Postmeal glycemic excursion was computed as the area under the CGM trace derived from the 24 glucose values in the 2-hour postprandial window. The resulting values in units of mg/dL*hr were divided by 24 so as to be on the same scale as point glycemic values in mg/dL (see Figure 1A). For example a glycemic excursion value of 100 mg/dL*hr denotes an average glucose level of 100 mg/dL during the 2-hour postprandial period. Postmeal hyperglycemia was defined as glycemic excursions greater than 180 mg/dL*hr based on the recommended ADA 2-hour postmeal target of 180 mg/dL.[1] Postmeal hypoglycemia was quantified as the number of sensor values at or falling below 70 mg/dL (the threshold for physiologic counterregulatory response, symptoms, and potentially acute clinical complications)[10] in the 2-hour postmeal period.

Individual Analysis

We limited the individual analysis to hyperglycemic excursions due to the low number of per-individual hypoglycemic events (see Table 1). As in the combined analysis, the prevalence of hyperglycemia (glycemic exposures greater than 180 mg/dL*hr) was tabulated according to positive and negative GS, but this time for each of the 240 subjects. An odds ratio and 95% CI was calculated for each individual.

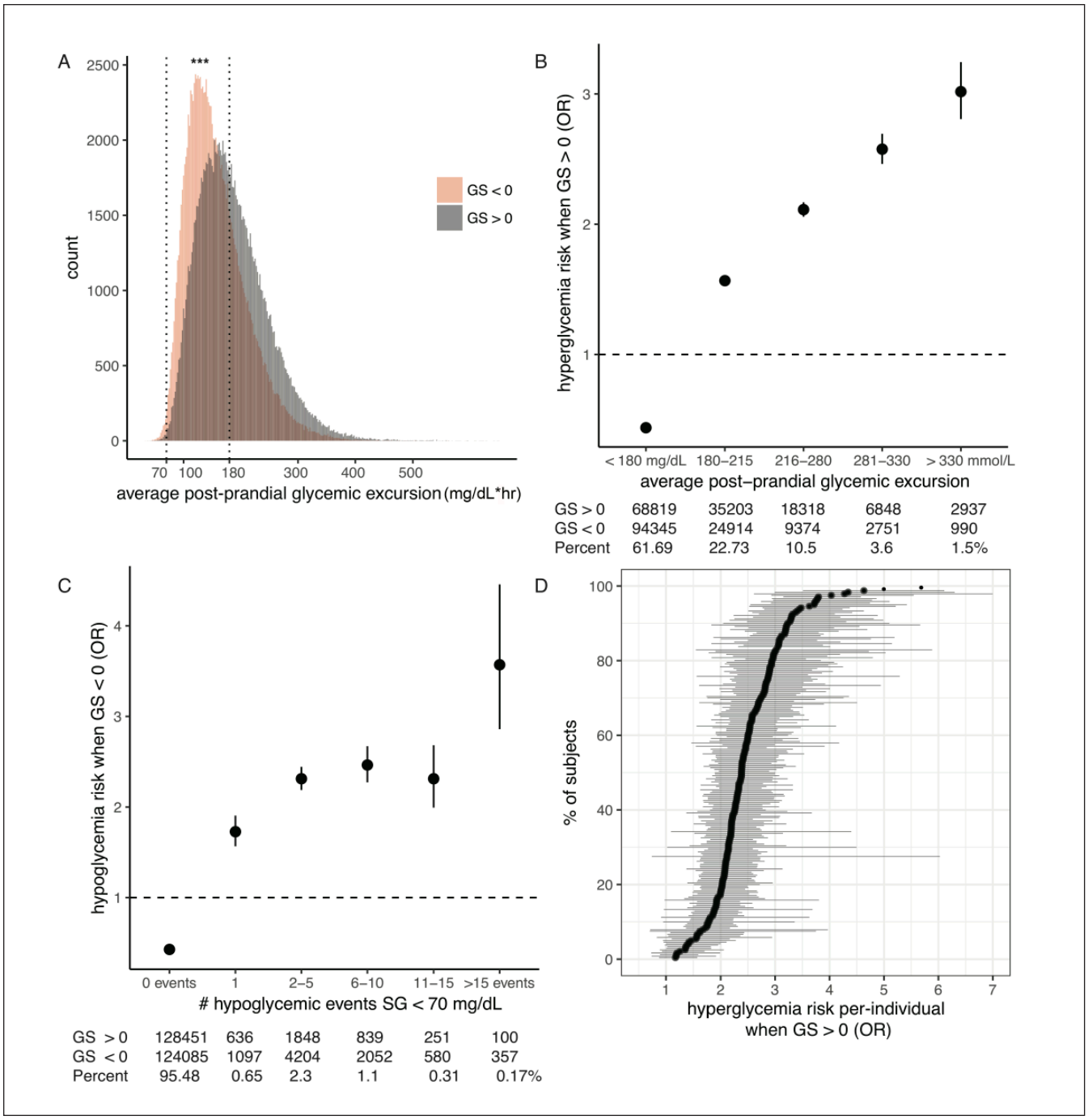

Figure 1. Relation of premeal glycemic slope (GS) and postprandial glycemic excursions. (A) Overlaid histograms of 2-hour postprandial glycemic excursions (ie, area under the curve of the sensor glucose trace) when preceded by positive (n = 132 125) or negative (n = 132 375) premeal GS. The dotted lines represent average glycemic excursions of 70 and 180 mg/dL *hr. ****P* < 2e-16 Kolmogorov–Smirnov test. (B) Risk of hyperglycemic excursions when preceded by positive GS. Each bin represents the average sensor glucose over 2 hours, the corresponding table of values indicates how many of the total 264 500 meals fell into each category. These were used to compute odds ratios and 95% confidence intervals as displayed. (C) Risk of hypoglycemic events when preceded by negative premedal GS. Each bin represents the number of occurrences of sensor glucose <70 mg/dL in the 2-hour postprandial period. The corresponding table indicates how many of the total 264 500 meals fell into each category. (D) For each subject (n = 240) an odds ratio and 95% confidence interval were computed for glycemic excursion >180 mg/dL*hr in relation to positive premedal GS. These are plotted in rank order of the odds radio estimate for each individual from low to high. Of individuals, 60% have an odds ratio between 2-3, with 40% displaying more sensitivity or less to premeal GS.

Table 1. Number of Data Points Extracted and Merged From 240 Subjects Enrolled in the STAR3 Study.

		Per subject	
	Total n = 240	Median (1st-3rd quartile)	
Sensor glucose values	23 572 818	107 300	(75 630-126 000)
Fingerstick blood glucoses	587 921	2334	(1740-2930)
Insulin boluses	694 715	2809	(2297-3537)
Meals[a]	264 500	1077	(661-1451)
Glycemic excursion >180 mg/dL*hr	10 135	153	(65-318)
Hypoglycemic events ≤70 mg/dL	11 964	32	(15-63)

[a]Meal denotes a carbohydrate count associated with an insulin bolus within 10 minutes. Postmeal glycemic excursions were measured as the area under the curve of the sensor glucose trace in the 2-hour postprandial window. Hypoglycemic events were tabulated in the 2-hour postprandial window.

Binning by Rate-of-Change Arrows Displayed to Patients on Commercially Available CGM Devices

Several commonly used CGMs (Abbott, Dexcom, Medtronic) display GS via rate-of-change arrows pointing up, down, and constant (Abbott and Dexcom).[5] Depending on the manufacturer, these arrows display magnitude and direction of GS in four to seven bins (eg, Dexcom: [<−3], [−3 to −2], [−2 to −1], [−1 to 1], [1 to 2], [2 to 3], [>3] mg/dL/min). The Dexcom platform displays the largest number of bins/arrows and these were selected for analysis of the STAR3 CGM data (obtained on the Medtronic Enlite sensor; see above). We tabulated postmeal glycemic excursions, hyperglycemia and hypoglycemia according to the bins underlying the rate-of-change arrows. In a subset analysis, we subdivided the "no change" bin ([−1 to 1] mg/dL/min) into positive ([−1 to 0] mg/dL/min) and negative ([0 to 1] mg/dL/min) GS bins and tabulated the occurrence of postmeal hyper- and hypoglycemia.

Statistical Methods

The Kolmogorov–Smirnov test was used to assess the difference and statistical significance of the distribution of glycemic excursions when preceded by negative or positive GS. Significance testing between means of nonnormally distributed glycemic excursions was performed by the nonparametric Wilcoxon rank sum test. The association of the sign of premeal GS and postmeal glycemic excursion was tested by logistic regression to obtain odds ratios and 95% confidence intervals. Statistical analyses and linear and logistic regressions were conducted using R programming language (R Foundation for Statistical Computing, https://www.R-project.org/).

Results

We aggregated and synchronized CGMS and pump data collected for one year on 240 subjects (see Table 1) to identify 264 500 "meals" (see Methods for definition) with accompanying insulin boluses and postmeal glycemic excursions. As described in the methods, the postmeal glycemic excursion value in mg/dL*hr indicates the actual glucose level integrated over 2 hours.

Table 2. Premeal Glycemic Slope (GS) Versus Positive Postmeal Glycemic Excursions.

	Glycemic excursion > 180 mg/dL*hr	Glycemic excursion ≤ 180 mg/dL*hr	All
GS > 0	63 306	68 819	132 125
GS < 0	38 029	94 346	132 375
Percentage	38.31	61.69	100

The sign of the GS was calculated from the sensor values 15 minutes prior to the meal. Postmeal glycemic excursions were measured as the area under the curve of the sensor glucose trace in the 2-hour postprandial window.

The observed distribution of postmeal glycemic excursions was bell-shaped with a large rightward skew reflecting an abundance of large glycemic excursions ("highs" vs "lows"). We examined the distributions of glycemic excursions in relation to positive and negative premeal glucose GS. Of the 264 500 meals, one-half (49.95%) were preceded by positive GS and the other half (50.05%) by negative GS. The distribution of postmeal glycemic excursions differed significantly when preceded by negative vs positive GS ($P < 2.2e\text{-}16$, Kolmogorov–Smirnov test). When preceded by negative GS, the mean postprandial glycemic excursion was 158.4 mg/dL*hr. When preceded by positive GS, it was 185.4 mg/dL*hr indicating that rising glucose levels prior to the meal resulted in an average excess glycemic exposure of ~27 mg/dL for 2 hours.

Taking a simple, unbiased approach, we next examined the relationship of positive and negative premeal GS in relation to postmeal hyperglycemia (glycemic excursions > 180 mg/dL*hr; see Figure 1B). Approximately 38% of postmeal glycemic excursions were in this hyperglycemic range. The prevalence of postmeal hyperglycemia was 2.28-fold (95% CI 2.25-2.32) greater when preceded by positive GS as compared to negative GS (see Table 2, Figure 1B). In addition to prevalence, the severity of postmeal hyperglycemia also increased when preceded by positive versus negative premeal GS (see Figure 1B). For example, positive premeal glycemic slope conferred a 3.02-fold (95% CI 2.81-3.24) increased risk of glycemic excursions greater than 330 mg/dL*hr.

Table 3. Premeal Glycemic Slope (GS) Versus Hypoglycemic Events.

	0 events ≤ 70 mg/dL	1 or more events ≤ 70 mg/dL	All
GS > 0	128 451	3674	132 125
GS < 0	124 085	8290	132 375
Percentage	95.48	4.523	100

The sign of the GS was calculated from the sensor values 15 minutes prior to bolus. Postmeal hypoglycemia was measured as the number of sensor glucose values ≤70 mg/dL in the 2-hour period following the meal.

We subsequently examined the relationship of positive and negative premeal GS in relation to postmeal hypoglycemic events (glucose ≤70 mg/dL in the 2 hours postprandially; see Figure 1C). Hypoglycemia in the postprandial period was a relatively infrequent event with less than 5% of meals followed by any sensor glucose values at or below 70 mg/dL in the 2-hour postprandial period (see Table 3, Figure 1C). However, negative versus positive premeal GS was associated with a 2.36-fold (95% CI 2.25-2.43) increase in at least one postprandial hypoglycemic event. Negative premeal GS also correlated with the frequency of postprandial hypoglycemic events (see Figure 1C). For example, negative premeal GS conferred a 3.98-fold (95% CI 2.93-5.41) increased risk of 15 or greater hypoglycemic values in the following 2 hours.

The per-individual analysis to examine the need for individualized "sensitivity factors" for GS incorporation into insulin dosing decisions showed individual odds ratios (OR) for postmeal hyperglycemia given positive versus negative premeal GS ranging from 1.2 to 5.7 (see Figure 1D). Of subjects, 60% had subject-specific OR ranging from 2 to 3. Notably, 20% of subjects showed diminished "GS sensitivity" with OR less than 2 and another 20% showed enhanced "GS sensitivity" with OR greater than 3.

We next categorized postmeal glycemic excursions for all 264 500 meals into GS bins corresponding to rate-of- change arrows commonly displayed by commercially available CGMs (see Figure 2A). With regard to positive glycemic excursions, a linearly increasing relationship was observed between "up" rate-of-change arrows and postmeal glycemic excursion. Membership in each increasing GS bin resulted in a stepwise increase of >20 mg/dL*hr of glycemic exposure. On the other hand, membership in negative GS bins corresponding to "down" rate of change arrows did not exhibit a clear relationship with glycemic exposure. Notably 76.2% of meals were preceded by GS in the "no change" ([–1, 1] mg/dL/min) bin as displayed to patients by their CGMs.

To assess whether this "no change" bin contained potentially clinically useful information that is hidden from the CGM user, we repeated our unbiased analysis relating positive and negative premeal GS in relation to hyperglycemic excursions and hypoglycemic events, this time considering only the 76.2% of meals (n = 201 549) meals preceded by GS in the [–1, 1] mg/dL/min range (see Figure 2A, "no change"). In this subset, when subdivided by negative versus positive GS, the distribution of postmeal glycemic excursions differed significantly ($P < 2.2e-16$, Kolmogorov–Smirnov test; Figure 2B). When preceded by negative GS, the mean postprandial glycemic excursion was 150 mg/dL*hr. When preceded by positive GS, it was 170 mg/dL*hr. In this subset, the presence of positive versus negative premeal GS still conferred a 1.82-fold (95% CI 1.79-1.86) increased risk of postmeal glycemic exposures greater than 180 mg/dL*hr. Conversely, negative versus positive premeal GS conferred a 2.06-fold (95% CI 1.99-2.15) increased risk of one or more postmeal hypoglycemic events.

Discussion/Conclusions

In this study we analyzed 240 patient-years of CGM and insulin pump data to examine the relationship of premeal glycemic slope (GS) and postmeal glycemic excursions. We found that positive premeal GS increased the risk of postmeal hyperglycemia and negative premeal GS increased the risk of postprandial hypoglycemic events. The relationship between premeal GS and postmeal glycemic excursions varied substantially by individual. We also found that the "no change" rate-of-change arrows on available CGM devices includes values (–1 to 1 mg/dL/min) that contain clinically useful information for postprandial hyper/hypoglycemia prediction.

The findings are statistically robust based on the large amount of glycemic, insulin bolus, and carbohydrate count data analyzed (Table 1). The outcome measured, integrated postmeal glycemic excursion, is clinically important not only as a contributor to overall glycemia but as an independent risk factor for cardiovascular complications.[11] By virtue of using the STAR3 data, our study benefits from uniform ascertainment, and is not confounded by factors such as variation in equipment and software since all subjects utilized the same pump, CGM, testing supplies and treatment algorithms.[7] However, the clinical homogeneity of subjects selected may also limit the generalizability of our findings, as does our retrospective design.

Notably, our findings were generated in a cohort of highly trained patients with type 1 diabetes who had already corrected for their meals based on premeal point glucose and carbohydrate count. Thus, premeal GS contains information independent of these commonly used dosing inputs and could enhance standard insulin dosing algorithms. To our knowledge, this study provides the first evidence for algorithmic incorporation of CGM-based glycemic trends into insulin dosing decisions in subjects with diabetes on basal-bolus insulin regimens.

Current expert guidelines suggest the use of GS to project future glucose levels and utilize this "anticipated glucose" in the premeal insulin bolus calculation.[5] Our study supports

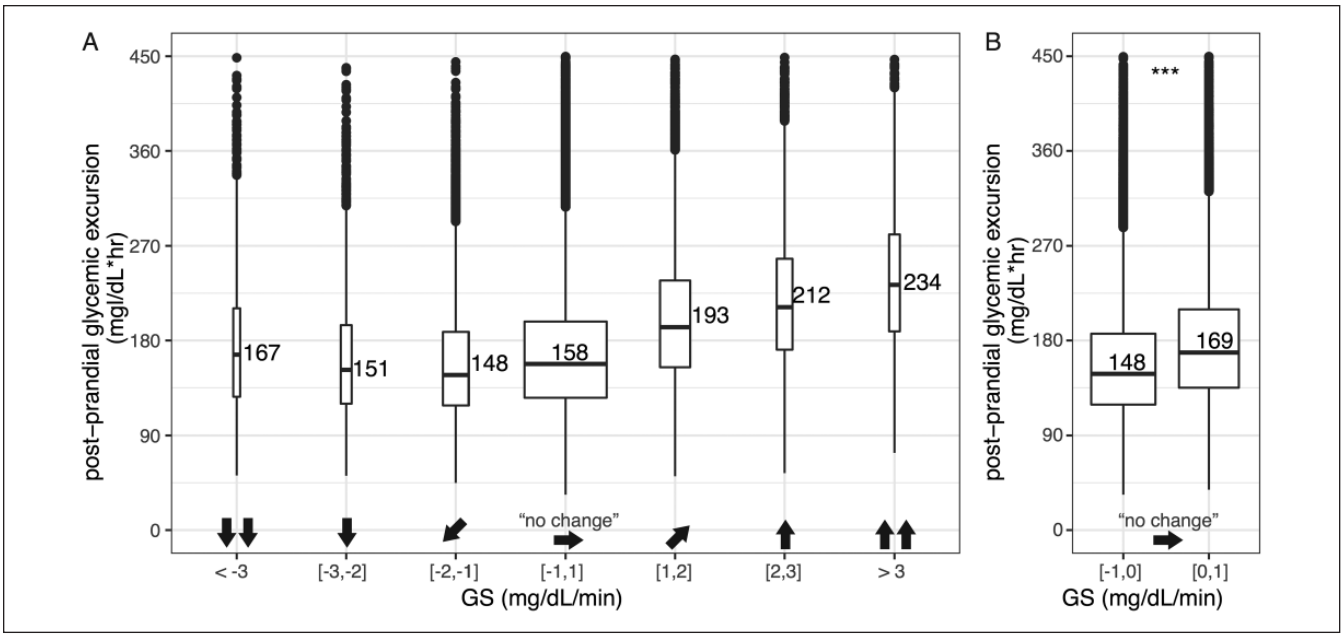

Figure 2. Premeal glycemic slope (GS) as displayed by CGM "rate-of-change arrows" and postprandial glycemic excursions. (A) Box and whisker plots with labeled median values of postprandial glycemic excursions binned according to rate-of-change arrows as commonly shown on available CGM devices. The width of the boxes is proportional to the number of meals in that bin (n = 1427, 3547, 19 557, 201 549, 27 302, 7468, 3539 from left to right). (B) The subject of meals (n = 201 549; 76.2% of total in the "no change" bin from (A) plotted according to positive and negative premeal GS. ***P < 2e-16 Wilcoxon rank sum test.

this approach with relation to positive GS and hyperglycemia. In our data, positive GS and glycemic excursions exhibit a dose-response relationship (Figure 2A) with postprandial hyperglycemia motivating the use of the actual GS value to "anticipate glycemic excursion" in combination with a patient-specific "GS-sensitivity" factor to increase insulin dose. Our analyses show wide individual variation in "GS-sensitivity" (odds ratios 1.2 to 5.7, see Figure 1D) suggesting that the incorporation of GS into dosing decisions should be personalized as is currently the standard with insulin sensitivity and carbohydrate ratios. With regard to hypoglycemia, negative GS irrespective of magnitude confers ~2-fold or greater risk of a postprandial hypoglycemic event (see Figure 1C) supporting a set reduction in the meal time insulin dose. Prospective studies will be required to validate and refine these suggestions.

Finally, our findings indicate that clinically actionable information is currently being hidden from CGM users due to binning artifacts encoded in the rate-of-change arrows on commercially available CGM devices. The cutoff of ±1 mg/dL/min is not based on physiology or empirical evidence, but simply a convenient round number. Our results support a redefinition of rate-of-change arrows that reports all positive and negative GS. Furthermore, this underscores the need to systematically examine the relationship between CGM-derived glycemic trends and outcomes to effectively and safely support dosing decisions. In summary, our study demonstrates that CGM-derived personal glycemic data contain robust and useful information that could be deployed in a systematic way to aid insulin dosing.

Abbreviations

CGM, continuous glucose monitoring; GS, glycemic slope; HbA1c, hemoglobin A1c; SG, sensor glucose; T1DM, type 1 diabetes mellitus.

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Declaration of Conflicting Interests

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