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Mitigation of Rebound Hyperglycemia With Real-Time Continuous Glucose Monitoring Data and Predictive Alerts

Giada Acciaroli, PhD[1], John B. Welsh, MD, PhD[1], and Halis Kaan Akturk, MD[2]

Abstract

Background: Excess carbohydrate intake during hypoglycemia can lead to rebound hyperglycemia (RH). We investigated associations between RH and use of real-time continuous glucose monitoring (rtCGM) and an rtCGM system's predictive alert.

Methods: RH events were series of sensor glucose values (SGVs) >180 mg/dL starting within two hours of an antecedent SGV <70 mg/dL. Events were characterized by their frequency, duration (consecutive SGVs >180 mg/dL × five minutes), and severity (area under the glucose concentration-time curve). To assess the impact of rtCGM, data gathered during the four-week baseline phase (without rtCGM) and four-week follow-up phase (with rtCGM) from 75 participants in the HypoDE clinical trial (NCT02671968) of hypoglycemia-unaware individuals were compared. To assess the impact of predictive alerts, we identified a convenience sample of 24 518 users of an rtCGM system without predictive alerts who transitioned to a system whose predictive alert signals an SGV ≤55 mg/dL within 20 minutes (Dexcom G5 and G6, respectively). RH events from periods of blinded versus unblinded rtCGM wear and from periods of G5 and G6 wear were compared with paired t tests.

Results: Compared to RH events in the HypoDE baseline phase, the mean frequency, duration, and severity of events fell by 14%, 12%, and 23%, respectively, in the follow-up phase (all $P < .05$). Compared to RH events during G5 use, the mean frequency, duration, and severity of events fell by 7%, 8%, and 13%, respectively, during G6 use (all $P < .001$).

Conclusions: Rebound hypreglycemia can be objectively quantified and mitigated with rtCGM and rtCGM-based predictive alerts.

Keywords

continuous glucose monitoring, glucose variability, HypoDE, predictive alerts, real-world analysis, rebound hyperglycemia

Introduction

In insulin-requiring diabetes, symptomatic hypoglycemia can motivate aggressive carbohydrate intake[1] beyond that needed to restore normoglycemia. Attempts to manage the resulting post-hypoglycemic hyperglycemia (rebound hyperglycemia, RH) may involve unsafe "rage bolus" doses of insulin[2] that contribute to high-amplitude swings in glucose levels. The phenomenon of RH has been documented in hospitalized patients with diabetes who were receiving intravenous insulin, where it was defined as any blood glucose level >180 mg/dL, with no requirement for antecedent hypoglycemia.[3] In this context, abrupt discontinuation of intravenous insulin led to RH in over 90% of the observed individuals. RH has also been observed in patients without diabetes after resection of insulinomas[4] or after enteral feeding.[5]

The use of continuous glucose monitoring (CGM) systems in diabetes management is increasing, and adoption of real-time CGM (rtCGM) systems is associated with sustainable improvements in hemoglobin A1c.[6,7] In adults with type 1 diabetes and impaired awareness of hypoglycemia, the HypoDE study[8] showed that access to rtCGM data was associated with significant reductions in the number of hypoglycemic events. In real-world observational studies,[9,10] further

[1]Dexcom, Inc., San Diego, CA, USA
[2]Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Corresponding Author:
John B. Welsh, MD, PhD, Dexcom, Inc., 6340 Sequence Drive, San Diego, CA 92121, USA.
Email: john.welsh@dexcom.com

Table 1. Rebound Hyperglycemia Events in the HypoDE Study.

	Preceding glucose nadir, mg/dL	Blinded phase	Follow-up phase	Relative difference (%)	*P* value
Frequency	<70	2.39 (1.62)	2.06 (1.49)	14	.027
(per week)	<55	1.04 (0.83)	0.75 (0.85)	28	.007
Duration (min)	<70	215 (217)	188 (186)	12	.022
	<55	205 (202)	198 (185)	3	.694
AUC >180 mg/dL	<70	15 476 (22 550)	11 961 (16 345)	23	.002
(mg/dL × min)	<55	15 437 (22 112)	12 432 (15 649)	19	.097

Note. RH events were defined as series of one or more sensor glucose values >180 mg/dL starting within two hours of a sensor glucose value <70 mg/dL or a subset of these events starting within two hours of a sensor glucose value <55 mg/dL. Results given as mean (SD).
Abbreviations: AUC, area under the (glucose concentration-time) curve; rtCGM, real-time continuous glucose monitoring.

hypoglycemia reductions were noted in association with use of alerts designed to warn users of impending hypoglycemia.

We sought to quantify RH in a group of HypoDE participants without and with access to rtCGM data and in a larger group of anonymized individuals who transitioned from routine use of an rtCGM system without predictive alerts to a system with a predictive alert.

Methods

Data from two different patient populations were used to evaluate the impact of rtCGM on RH and, separately, to evaluate the impact of an rtCGM-based predictive alert on RH. The first population was 75 participants in the HypoDE clinical trial (NCT02671968), the methods[11] and primary outcomes[8] of which are published separately. Briefly, HypoDE was a multicenter randomized controlled trial that enrolled participants with type 1 diabetes and problematic hypoglycemia (evidenced by either impaired hypoglycemia awareness or a recent history of severe hypoglycemia) who were using multiple daily insulin injections. Data were collected from a four-week pre-randomization phase in which rtCGM (G4 with Software 505, Dexcom, Inc., San Diego, CA) data were not visible to participants. After a 22-week therapy phase, the 75 participants underwent a four-week follow-up phase of rtCGM (G5, Dexcom) use; data from the pre-randomization and follow-up phases were compared. The second population was 24 518 US-based users of an rtCGM without a predictive hypoglycemia alert (G5) who transitioned to an rtCGM system with such an alert (G6, Dexcom). The G6 System features an optional "urgent low soon" (ULS) alert that is enabled by default and is triggered by series of sensor glucose values (SGVs) that are predicted to reach ≤55 mg/dL within 20 minutes. Data from customers who had uploaded ≥30 days of data from each system in the 2018 calendar year were considered. To minimize nonspecific effects of the transition, only users who had between-system data gaps of less than seven days were included.

An RH event was defined as any series of one or more SGVs >180 mg/dL preceded by any series of one or more SGVs <70 mg/dL, with the condition that the first SGV in the hyperglycemic series occurred within two hours of the last value in the hypoglycemic series. RH events were characterized by their weekly frequency, duration in minutes, severity (area under the curve [AUC] in mg/dL × minutes), and time of onset with respect to the most recent hypoglycemic SGV. RH events starting within two hours of an SGV <55 mg/dL formed a subset of events that were analyzed separately.

The blinded and unblinded phases of the HypoDE study were compared in terms of frequency, duration, and AUC of the RH events following a hypoglycemic event with an SGV nadir value below 70 mg/dL or following a subset of those events with an SGV nadir value below 55 mg/dL. Statistical significance of the within-patient comparisons between the blinded and unblinded phases was assessed with paired t tests. The G5 and G6 phases of users transitioning from G5 to G6 were compared in terms of frequency, duration, and AUC of the RH events following a hypoglycemic event with an SGV nadir value below 70 mg/dL or following a subset of those events with an SGV nadir value below 55 mg/dL. Statistical significance of the within-patient comparisons between the G5 and G6 phases was assessed with paired t tests. To compare RH frequency and duration among cohorts of users with high and low glycemic variability during their G6 use, coefficients of variation (CVs) were calculated for each individual and the summary statistics for those in the highest and lowest CV quartiles were compared.

Ethical approval was granted for the HypoDE trial, and informed consent was obtained from its participants. The analysis of customer data was consistent with Dexcom's Privacy Policy[12] and, since all patient identifiers were removed before data analysis was begun, it was not registered as a trial.

Results

Tables 1 and 2 summarize RH events and hypoglycemic events from the blinded and unblinded phases of the HypoDE clinical trial. Compared to the baseline phase, Table 1 shows

Table 2. Hypoglycemic Events in the HypoDE Study.

	Glucose nadir, mg/dL	Blinded phase	Follow-up phase	Relative difference (%)	*P* value
Frequency (per week)	<70	10.02 (5.55)	6.47 (4.55)	35	.027
	<55	5.42 (4.30)	2.18 (2.31)	60	.007
Duration (min)	<70	73 (83)	45 (42)	38	<.001
	<55	57 (70)	34 (34)	41	<.001
AUC <70 mg/dL (mg/dL × min)	<70	971 (1792)	411 (728)	58	<.001
	<55	489 (929)	211 (390)	57	<.001

Note. Results given as mean (SD).
Abbreviations: AUC, area under the (glucose concentration-time) curve; rtCGM, real-time continuous glucose monitoring.

Table 3. Rebound Hyperglycemia Events in Users of the G5 and G6 Systems.

	Preceding glucose nadir, mg/dL	G5	G6	Relative difference (%)	*P* value
Frequency (per week)	<70	1.83 (1.30)	1.70 (1.36)	7	<.001
	<55	0.78 (0.68)	0.52 (0.59)	33	<.001
Duration (min)	<70	214 (142)	197 (151)	8	<.001
	<55	219 (161)	171 (190)	22	<.001
AUC >180 mg/dL (mg/dL × min)	<70	15 601 (17 936)	13 638 (17 527)	13	<.001
	<55	16 741 (21 338)	12 283 (21 669)	27	<.001

Note. RH events were defined as series of one or more sensor glucose values >180 mg/dL starting within two hours of a sensor glucose value <70 mg/dL or a subset of these events starting within two hours of a sensor glucose value <55 mg/dL. Results given as mean (SD).
Abbreviations: AUC, area under the (glucose concentration-time) curve.

Table 4. Hypoglycemic Events in Users of the G5 and G6 Systems.

	Glucose nadir, mg/dL	G5	G6	Relative difference (%)	*P* value
Frequency (per week)	<70	4.74 (4.21)	4.26 (4.24)	10	<.001
	<55	1.58 (2.03)	1.02 (1.60)	36	<.001
Duration (min)	<70	48 (24)	40 (20)	17	<.001
	<55	39 (20)	30 (32)	23	<.001
AUC <70 mg/dL (mg/dL × min)	<70	542 (391)	397 (346)	27	<.001
	<55	331 (251)	242 (388)	27	<.001

Note. Results given as mean (SD).
Abbreviations: AUC, area under the (glucose concentration-time) curve.

that RH events in the unblinded follow-up phase were less frequent, did not last as long, and were not as severe. The relative reduction was largest for the duration of RH events that were preceded by one or more SGVs less than 55 mg/dL. Table 2 shows that the frequency, duration, and severity of hypoglycemic events was reduced in the unblinded follow-up phase. Based on their weekly frequencies, fewer than half of the hypoglycemic events were followed by RH events.

Tables 3 and 4 provide results for RH events and hypoglycemic events experienced by 24 518 uploaders who sequentially used the G5 and G6 systems and retained the G6 ULS feature in its default (enabled) state. Compared to G5 use, Table 3 shows that RH events during G6 use were less frequent, did not last as long, and were not as severe; the relative reductions were larger for RH events preceded by one or more SGVs less than 55 mg/dL. Table 4 shows that the frequency, duration, and severity of hypoglycemic events were all lower during G6 use than during G5 use, with relative reductions ranging from 10% to 27%.

There were no significant correlations between the duration of antecedent hypoglycemia and either the duration or severity of subsequent RH events in either the HypoDE data set or the customer data set (not shown). The mean (SD) time intervals between the last SGV <70 mg/dL and the first SGV >180 mg/dL value for RH events in the HypoDE study's blinded and unblinded phases were 68.65 (27.04) and 68.55 (27.56) minutes, respectively, a relative difference of <1% ($P = .95$). The time intervals between the last SGV <70 mg/

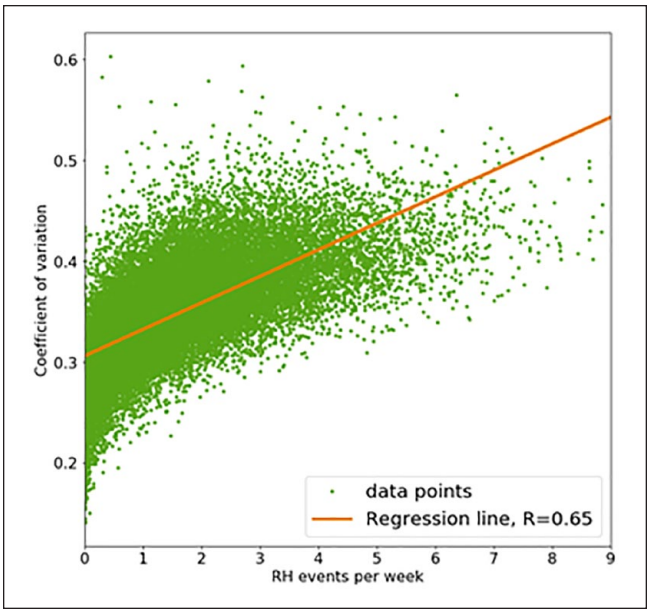

Figure 1. The relationship between CV and RH event frequency among 24 518 people during use of the G6 rtCGM system. The correlation during G5 use (not shown) was similarly strong (r = 0.64). CV, coefficient of variation; RH, rebound hyperglycemia.

dL and the first SGV >180 mg/dL for RH events during G5 and G6 use were 73.63 (10.54) and 71.28 (19.55) minutes, respectively, a relative difference of 3% ($P < .001$).

Using data from the same patients described in Tables 3 and 4, Figure 1 shows the strong positive (r = 0.65) correlation between CV and the weekly frequency of RH events during G6 use; the correlation during G5 use was similar (r = 0.64). During G6 use, users with CVs in the lowest quartile ("stable," CV <32%) were compared to users with CVs in the highest quartile ("labile," CV >39%) with respect to RH frequency and duration. RH events in the stable group were much less frequent (0.55 ± 0.56 vs 2.90 ± 1.45 episodes per week) and were of significantly shorter duration (162 ± 208 vs 209 ± 99 minutes) than RH events in the labile group ($P < .001$ for each comparison).

Discussion

Using a simple scheme to quantify episodes of RH, data presented here show that they can be mitigated or avoided by either adoption of rtCGM or adoption of an rtCGM system with a predictive hypoglycemia alert. Because the HypoDE study's primary outcome was the rate of hypoglycemic episodes and the primary motivation for the predictive hypoglycemia alert feature was hypoglycemia reduction, attenuation of RH was unexpected. In both data sets, we observed reductions in the frequency of RH events, which may be partially attributable to reductions in hypoglycemia. However, observed reductions in the mean duration and severity of RH events are likely independent of changes in the frequency of the antecedent hypoglycemic events. The strong relationship between RH frequency and CV is an additional finding of this study, and suggests that RH may be an important contributor to short-term glycemic instability.

The prominent role played by counterregulatory hormones such as catecholamines and glucagon in the normal response to hypoglycemia is disrupted in type 1 diabetes,[13,14] and type 1 diabetes duration has been associated with impaired glucagon secretion.[15] In patients with hypoglycemia unawareness, counterregulatory hormonal response is further altered, and the threshold for a response is decreased.[16] Considering that the HypoDE study was conducted in a population enriched for hypoglycemia unawareness, we believe that the effect of counterregulatory hormones was minimal and the RH events may likely be explained with overcorrections.

Management of acute hypoglycemia is made more difficult by specific cravings for carbohydrate-rich foods[1] and cognitive impairment.[17] Consequent episodes of RH may prompt detrimental "rage bolusing" of insulin, followed by "roller-coastering" and "crashing"[2] of glucose concentrations, which may be more dangerous than sustained hyperglycemia.[18]

Users of rtCGM systems may further benefit from alerts triggered by impending hypoglycemia. Use of the predictive alerts in the Guardian Connect CGM system (Medtronic, Inc., Northridge, CA) was associated with prevention of 59% of low excursions and 39% of high excursions.[9] Use of Dexcom's ULS feature, combined with a low threshold alert, was associated with significantly fewer low glucose readings.[10] For users of insulin pumps, automated features such as "Suspend Before Low" serve the dual purpose of reducing hypoglycemia (by stopping insulin in the face of existing or impending hypoglycemia) and minimizing subsequent RH episodes (by resuming insulin delivery once the hypoglycemia has resolved).[19]

A strength of the HypoDE study was its design, which allowed for within-individual comparisons, and its narrow focus on individuals with type 1 diabetes and problematic hypoglycemia. Strengths of the present analysis of real-world G5 and G6 users include the high density of available data, the large number of observed individuals, and the ability to make within-individual comparisons of RH events during G5 versus G6 use. The study also has several limitations. Importantly, we do not know how HypoDE clinical trial participants used the rtCGM data, and although hypoglycemia education programs were offered to all participants, completion of an educational program was not an inclusion criterion. Similarly, we do not know how anonymized G6 users responded to activations of the ULS feature. We made no attempt to characterize other alert settings. Patient-level decisions surrounding RH events, especially those related to insulin dosing and carbohydrate intake, are similarly unknown. Our choice of the glucose concentrations and time intervals for defining RH events differs from earlier definitions that were not based on CGM data[3] or did not require antecedent hypoglycemia.[3,5] We chose 180 mg/dL as the

lower boundary for hyperglycemia to be consistent with consensus guidelines.[20,21] Separately, a recent analysis of discriminant ratios[22] proposed 180 mg/dL as the ideal threshold value for hyperglycemia. Additionally, our definition is consistent with the algorithm used by Dexcom's CLARITY software[23] for retrospective CGM data analysis, where RH events are identified on the "Overlay," "Daily," and "Compare" CLARITY report types. Factors that contribute to RH events, the ability of automated insulin delivery systems to mitigate or prevent them, and their clinical implications are topics of further study.

Conclusion

Because RH events are easily visualized and quantified, patients may be well-motivated to associate them with choices related to avoiding and managing hypoglycemia, when it does occur, without overtreatment. Because of the strong correlation between RH and CV, adjustments aimed at reducing RH events are likely to reduce glycemic variability, which may have important clinical and therapeutic implications.[24,25] The favorable reductions in RH event frequency, duration, and severity that are associated with rtCGM use and with use of an rtCGM-based predictive alert for hypoglycemia highlight another way in which these technologies provide actionable insights for people with diabetes.

Abbreviations

AUC, area under the glucose concentration-time curve; CGM, continuous glucose monitoring; CV, coefficient of variation; RH, rebound hyperglycemia; SGV, sensor glucose value; ULS, urgent low soon.

Authors' Note

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ORCID iDs

John B. Welsh https://orcid.org/0000-0001-9243-5228

Halis Kaan Akturk https://orcid.org/0000-0003-4518-5179

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