The Effect of Glycemic Variability on Counterregulatory Hormone Responses to Hypoglycemia in Young Children and Adolescents with Type 1 Diabetes

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Abstract

Background: Glycemic variability (GV) is associated with hypoglycemia and possibly diabetes-related outcomes. We hypothesized that GV and glucose excursion risk may predict counterregulatory (CR) hormone responses to hypoglycemia.

Research Design and Methods: This is a secondary analysis of a Diabetes Research in Children Network study containing continuous interstitial glucose monitoring records for 28 patients with type 1 diabetes between 3 to <8 or 12 to <18 years of age. GV and excursion measures, including continuous overall net glycemic action (CONGA), High Blood Glucose Index (HBGI), Low Blood Glucose Index (LBGI), and coefficient of variation (CV), were calculated 72 h prior to insulin-induced hypoglycemia. CR hormones were measured during the progressive fall in plasma glucose.

Results: CV was inversely correlated with change in glucagon concentration ($r = -0.41$, $P = 0.046$), but CONGA (log-transformed for better fit of the models) was not statistically significant in univariate analysis ($r = -0.34$, $P = 0.10$). Other CR hormones were not significantly associated with measures of variability. In multivariate analysis, higher CONGA, but not CV, was associated with a smaller rise in glucagon following induced hypoglycemia (estimate = -9.73 , $P = 0.048$), independent of hemoglobin A1c, duration of diabetes, and insulin dose. HBGI, LBGI, and antecedent time spent in hypoglycemia were not significantly correlated with CR response to subsequent hypoglycemia.

Conclusions: CV and CONGA may be predictors of impaired glucagon responses to insulin-induced hypoglycemia in patients with type 1 diabetes. Further study is indicated to characterize the role of GV and glycemic excursions on the defensive response to hypoglycemia.

Introduction

ALTHOUGH IT HAS LONG BEEN established that sustained chronic hyperglycemia leads to microvascular complications, the effects of acute glycemic fluctuations are less well documented. Emerging data supporting a role for glycemic variability (GV) in the development of micro- and macrovascular complications are conflicting, in part because of the limitations of self-monitored blood glucose in assessing GV, a lack of consensus for the measurement of GV, and a lack of prospective data on outcomes.¹

Among the reasons supporting integration of measures of GV into a global diabetes strategy is its potential for predicting hypoglycemia. Notable increases in GV precede the occurrence of severe hypoglycemic episodes.² Hypoglycemia

normally leads to counterregulatory (CR) release of plasma catecholamines and glucagon. However, in patients with diabetes who have hypoglycemia-associated autonomic failure (HAAF), the plasma glucose threshold stimulating such release is reduced. Glucagon responses are lost early on likely because of the absence of intra-islet insulin signal in insulin-deficient diabetes, and sympathetic responses to repeated episodes of hypoglycemia are subsequently reduced, resulting in increased risk for severe hypoglycemia.³ In addition to the immediate adverse consequences of hypoglycemia, HAAF leads to increased fear and pattern of maladaptive behaviors that propagate worsening overall control.⁴

The Diabetes Research in Children Network (DirecNet) Study group recently reported that even children and adolescents with type 1 diabetes are prone to developing HAAF.⁵

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We analyzed this DirecNet data set to determine whether antecedent GV and glucose excursion risk are predictive of impaired CR hormone responses to hypoglycemia in this population of young subjects with type 1 diabetes.

Research Design and Methods

The investigation uses a de-identified public data set compiled by the DirecNet Study Group for secondary analysis.⁵ The details of procedures for the study have been described previously.⁶ Twenty-eight subjects 3 to <8 or 12 to <18 years old with type 1 diabetes were enrolled. Eligibility criteria included duration of type 1 diabetes of at least 1 year, hemoglobin A1c (HbA1c) <10%, and use of a continuous subcutaneous insulin infusion. Subjects were excluded if they had cystic fibrosis or if, during the last month, they had had a severe hypoglycemic event resulting in seizure or loss of consciousness or had used corticosteroids. Each was hospitalized overnight at one of the five DirecNet clinical centers after having worn a Guardian® real-time continuous glucose monitoring (CGM) device (Medtronic Minimed, Northridge, CA) for 1 week at home.

Upon admission of the patient, a peripheral intravenous catheter was inserted for blood sampling. A bolus dose of insulin equal to approximately 1 h of the subject's basal rate was given at the start of the test, and the basal insulin infusion rate was increased by 25–50% or as needed to gradually drop glucose levels. Meter glucose measurements were checked every 15 min until glucose was less than 100 mg/dL, at which time they were obtained at 5–10-min intervals.⁷ Blood samples were collected for glucose, glucagon, cortisol, growth hormone (GH), epinephrine, norepinephrine, and dopamine concentrations at baseline glucose levels between 95 to 110 mg/dL and then following subcutaneous insulin-induced hypoglycemia when glucose levels were <90, <80, <70, and <60 mg/dL. Intravenous glucose and breakfast were given once the glucose level was <60 mg/dL and the basal rate was returned to normal. An additional blood sample was collected 15 min after administration of intravenous glucose. Institutional Review Board approval was obtained at each center, and written consent and assent were given by the parent/guardian and each patient older than 7 years, respectively.⁶ To provide a reference to judge the responses to hypoglycemia in patients with type 1 diabetes, the epinephrine responses to a similar degree of hypoglycemia in 14 adolescents (12–17 years of age) without diabetes who had been assessed during studies performed at the Children's Hospital of Pittsburgh (Pittsburgh, PA) were reported.⁶

Measures of GV and mean glucose were calculated using available interstitial glucose levels in the 72 h prior to admission. For assessment of GV we calculated continuous overall net glycemic action (CONGA) and coefficient of variation (CV). CONGA describes intra-day glycemic variation using the SD of difference of successive sensor glucose values that are 1 h apart. The CONGA value is a measure suitable for ambulant CGM systems with higher values reflecting increased GV and less stable control.⁸ The range for CONGA was 30.6–57.6 in subjects with type 1 diabetes and 7.2–21.6 for controls in a small study of children.⁶ High Blood Glucose Index (HBGI) and Low Blood Glucose Index (LBGI) were calculated using the first measurement of each hour during the 72 h prior to the clinic visit. LBGI and HBGI are measures of glycemic excursion or risk of hypoglycemia and hyperglycemia, respectively.⁹ The risks of hypoglycemia and hyperglycemia were categorized as follows

based on self-monitored glucose data compiled from 335 subjects with type 1 or 2 diabetes: LBGI, minimal (LBGI <1.1), low (1.1 < LBGI <2.5), moderate (2.5 < LBGI <5), and high (LBGI >5); HBGI, low (HBGI <4.5), moderate (4.5 < HBGI <9), and high (HBGI >9).¹⁰ These blood glucose indices are components of the average daily risk range, a validated predictor of high and low glucose extremes, but less optimally suited for CGMS than its components.¹

Statistical analysis

Correlations were performed between CV, CONGA, HBGI, LBGI, or time spent in hypoglycemia (<70 mg/dL on CGM) in the 72 h prior to hospitalization and change in hormone concentration from baseline to peak following insulin-induced hypoglycemia. A multivariable model using backwards linear least squares regression was completed for predictors of glucagon. CONGA was log-transformed for better fit of the models. Furthermore, subjects were stratified by median CV, CONGA, HBGI, and LBGI and analyzed according to the proportion of subjects who had hormone responses, defined as an increase in hormone concentration >3 SD above baseline (with the SD based on the duplicate blood samples at baseline).⁶ The 3 SD limits were 26 pg/mL for epinephrine, 44 pg/mL for norepinephrine, 0.83 µg/dL for cortisol, 1.2 ng/mL for GH, and 16 pg/mL for glucagon, as outlined previously.⁶ Comparisons of continuous and dichotomous variables were performed using a one-way analysis of variance and Fisher's Exact test, respectively, with $P < 0.05$ considered statistically significant.

Results

Demographic characteristics of the 14 children (4–7 years old) and 14 adolescents (12–17 years old) in the DirecNet dataset included 32% female and 91% white (Table 1). The mean HbA1c was 7.69%, mean duration of diabetes was 5.2 years, and the mean time spent in hypoglycemia 72 h prior to insulin-induced hypoglycemia was 138 min. In the week prior to admission, patients or parents reported an average of 2.35 episodes of hypoglycemia. The mean LBGI was 5.95, whereas the mean HBGI was 32.59. The mean CONGA score was 46.

In total, the numbers of subjects who mounted a CR hormone response to insulin-induced hypoglycemia at a level <60 mg/dL for glucagon, epinephrine, GH, cortisol, and norepinephrine were one, 17, 20, five, and 13, respectively. The remainder never expressed a CR hormone response to hypoglycemia. Analysis of the change in CR hormone following insulin-induced hypoglycemia was further stratified by gender. There were statistically insignificant differences in CR responses between genders (in females vs. males, change in glucagon was -3.29 vs. 2.19 pg/mL [$P = 0.11$], change in cortisol was 0.81 vs. 0.19 µg/dL [$P = 0.67$], change in GH was 23.5 vs. 20.7 ng/mL [$P = 0.85$], change in epinephrine was 23.4 vs. 73.0 pg/mL [$P = 0.07$], and change in norepinephrine was 65.4 vs. 67.7 pg/mL [$P = 0.93$]).

Correlations between antecedent hypoglycemia and CR hormone response to subsequent induced hypoglycemia

The antecedent time spent in hypoglycemia was not significantly correlated with the CR hormone responses to subsequent induced hypoglycemia (Table 2). There was,

TABLE 1. PATIENT CHARACTERISTICS

Demographic (n=28)	
Race	
African American	1 (3.5%)
White	26 (91%)
Hispanic	1 (3.5%)
Age	
Young children (4–7 years)	14 (50%)
Adolescents (12–17 years)	14 (50%)
Gender	
Male	19 (67.9%)
Female	9 (32.1%)
Weight (kg)	40.64 (22.63)
Duration of type 1 diabetes (years)	5.16 (3.00)
Total daily insulin dose (units/kg)	0.79 (0.22)
Glycemic variables	
HbA1c (%)	7.69 (0.79)
Time in hypoglycemia (<70 mg/dL)	138.21 (208.71)
72 h prior to induced hypoglycemia (min)	
CONGA (mg/dL)	46.3 (17.55)
HBGI	32.59 (9.49)
LBGI	5.95 (5.57)
Baseline CR hormones	
Glucagon (pg/mL)	43.73 (11.91)
Cortisol (μg/dL)	11.16 (3.22)
Growth hormone (ng/mL)	4.42 (6.16)
Epinephrine (pg/mL)	41.50 (17.81)
Norepinephrine (pg/mL)	142.43 (49.90)

Data are number (%) or mean (SD) values as indicated.

CONGA, continuous overall net glycemic action; CR, counter-regulatory; HbA1c, hemoglobin A1c; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index.

however, a significant difference in the change in glucagon level following hypoglycemia between patients who did or did not self-report hypoglycemia in the week prior to admission (-3.35 vs. 4.21 pg/mL, $P=0.048$). Otherwise, there was no difference in the change in CR hormone responses to hypoglycemia in patients with or without self-reported antecedent hypoglycemia (data not shown).

Correlations between GV/excursion and CR hormone response to subsequent induced hypoglycemia

CV had a weak but significant inverse correlation with change in glucagon following insulin-induced hypoglycemia

($r = -0.41$, $P=0.046$), such that higher CV was associated with a smaller increment in glucagon (Table 2). Log-transformed CONGA also had a similar weak inverse correlation with change in glucagon, but this was not statistically significant ($r = -0.34$, $P=0.10$). Other CR hormones were not significantly associated with measures of variability. LBGI and HBGI were not significantly correlated with the change in any CR hormone following insulin-induced hypoglycemia (Table 2).

A multivariable model was created, including gender, HbA1c, insulin dose/kg, duration of diabetes, and either CONGA or CV as independent variables and glucagon response to insulin-induced hypoglycemia as the dependent variable. Using a backwards stepwise approach, the final model showed that log CONGA was a significant predictor of the glucagon response (estimate = -9.73 , $P=0.048$), independent of insulin dose/kg, HbA1c, and duration of diabetes (Table 3). Gender was not a significant predictor ($P=0.38$). When CV was substituted for CONGA in the multivariable model, however, it was not found to be a significant predictor of the glucagon response (estimate = -0.33 , $P=0.19$).

Bivariate analyses of GV and CR response to subsequent induced hypoglycemia

Subjects were stratified based on median CONGA, CV, HBGI, and LBGI for a comparison of the number of responders with an increase of >3 SD from baseline level of each of the hormones ($P>0.05$ for all comparisons). HBGI significantly predicted an inadequate CR hormone response to epinephrine as shown by data in Table 4. Only four subjects with HBGI above the median of 33 (mean, 40.250 ± 4.725) had an epinephrine response compared with 13 of those with HBGI below median ($P=0.0005$). The difference in cortisol response among subjects in the two groups was also significant ($P=0.05$), with five responding in the lower HBGI group (mean, 24.923 ± 6.168) and none among those with HBGI above median. There was no difference in glucagon, GH, or norepinephrine response with respect to median HBGI, and there was no difference in any CR hormone response with respect to median LBGI, CV, and CONGA.

Conclusions

The overall aim of this analysis was to determine whether GV is associated with the defensive CR hormone response against hypoglycemia. Our hypothesis was that antecedent GV would blunt this response. We found that increasing

TABLE 2. PAIRWISE CORRELATIONS BETWEEN COEFFICIENT OF VARIATION, HIGH BLOOD GLUCOSE INDEX, LOW BLOOD GLUCOSE INDEX, LOG CONTINUOUS OVERALL NET GLUCOSE ACTION, ANTECEDENT HYPOGLYCEMIA, AND CHANGE IN COUNTERREGULATORY HORMONE RESPONSES TO INDUCED HYPOGLYCEMIA

	CV		HBGI		LBGI		Log CONGA		Antecedent hypoglycemia	
	r	P value	r	P value	r	P value	r	P value	r	P value
Glucagon	-0.41	0.046	-0.21	0.33	-0.35	0.09	-0.34	0.10	-0.26	0.20
Epinephrine	-0.35	0.08	-0.26	0.21	-0.22	0.29	-0.31	0.14	-0.20	0.31
Growth hormone	0.09	0.67	0.25	0.22	-0.09	0.66	0.26	0.20	-0.18	0.35
Cortisol	-0.09	0.69	-0.07	0.74	-0.17	0.45	0.06	0.79	-0.07	0.75
Norepinephrine	-0.07	0.75	0.16	0.48	0.18	0.42	-0.03	0.91	0.08	0.72

CONGA, continuous overall net glycemic action; CV, coefficient of variation; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index.

TABLE 3. PREDICTORS OF GLUCAGON RESPONSE TO HYPOGLYCEMIA

Term	Estimate	SE	P value
HbA1c (%)	19.88	8.42	0.0291
Duration of DM (years)	-28.44	12.04	0.0290
Insulin dose/weight (units/kg)	227.02	96.15	0.0291
log CONGA (mg/dL)	-9.73	4.60	0.0481

Data analyses were performed using multivariate backwards linear model using least squares regression.

CONGA, continuous overall net glucose action; DM, diabetes mellitus; HbA1c, hemoglobin A1c.

CV was a predictor of the glucagon response to insulin-induced hypoglycemia in univariable analysis, but only CONGA was a significant predictor in multivariable analysis.

The differential results obtained from analysis of CONGA and CV may be due to differences in properties of the two measures of GV. CONGA is able to account for rate of change by calculating hourly differences in successive glucose measurements, whereas CV calculates only the difference from the overall mean (not rate of change). One could speculate that the rate of change in glucose, in addition to the degree of hypoglycemia, affects the CR response. Previous studies in which glucose levels were experimentally reduced at variable rates over a short period of time under controlled conditions do not support this possibility.¹¹⁻¹³ However, it may be possible that repeated large glucose excursions over a longer period of time, as in this patient population, are necessary to have an effect on the CR response. Limited data support a role for experimentally induced glucose oscillations in the development of endothelial dysfunction and oxidative stress, independent of sustained hyperglycemia or hypoglycemia.^{14,15} Therefore, a differential physiologic role for sustained hyperglycemia, intermittent hyperglycemia, and hypoglycemia is not unprecedented.

The observation that hypoglycemia was not a predictor of the CR hormone response is somewhat unexpected. The discrepancy may be explained by lower accuracy of CGM in the hypoglycemic range¹⁶ and the need for a longer time period to acquire enough hypoglycemic events for analysis. Hypoglycemia has been shown to blunt the CR hormone responses to subsequent hypoglycemia and begets HAAF.¹⁷ Patients with self-reported hypoglycemic events did have an attenuated glucagon response to hypoglycemia. However, glucagon responses are lost early after the diagnosis of type 1 diabetes, likely because of the absence of intra-islet insulin signaling, and may not be the result of HAAF. As reported previously, a large percentage of subjects in this sample failed to demonstrate any response even with a glucose level <60 mg/dL, regardless of average daily risk range components, CV, or CONGA levels. The GH response was the one exception, which, unlike epinephrine, norepinephrine, and glucagon, increased with increasing measures of GV, raising the question of whether GH responses are augmented in response to increased GV. One explanation for this is that GH may serve as a compensatory mechanism for the loss of other CR hormone responses.¹⁸ However, this finding must be interpreted with caution, and considering the complex hormonal changes that occur during puberty, it may not be generalized to other

TABLE 4. COMPARISON OF COUNTERREGULATORY HORMONE RESPONDERS STRATIFIED BY MEDIAN MEASURE OF GLYCEMIC VARIABILITY AND EXCURSION

	CV (median = 36.46)			HBGI (median = 33)			LBGI (median = 4.36)			CONGA (median = 46.69)		
	Above median (n=13)	Below median (n=13)	P value	Above median (n=13)	Below median (n=13)	P value	Above median (n=13)	Below median (n=13)	P value	Above median (n=13)	Below median (n=13)	P value
Glucagon	1	0	0.99	1	0	0.99	1	0	0.99	1	0	0.99
Epinephrine	7	10	0.41	4	13	0.0005	7	10	0.41	9	8	0.99
Growth hormone	10	10	1.0	8	12	0.16	11	9	0.64	10	10	1.0
Cortisol	3	2	0.99	0	5	0.05	3	2	0.99	2	3	0.99
Norepinephrine	6	7	0.99	4	9	0.12	7	6	0.99	7	6	0.99

Data are *n* where *n* = number of subjects with a counterregulatory hormone response (defined as an increase of >3 SD from baseline level) to induced hypoglycemia. Analyses were performed using Fisher's exact test.

CONGA, continuous overall net glucose action; CV, coefficient of variation; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index.

age groups. In a previous report in children, spontaneous nocturnal hypoglycemia stimulated small increases in GH that were not an effective defense against hypoglycemia.¹⁹ Unlike the results for the continuous analysis of glycemic measures, the dichotomous analysis did not demonstrate differences in the glucagon response to hypoglycemia for any of the glycemic measures, most likely due to the small sample size. Although HBGI (in dichotomous analysis) was associated with lower epinephrine responses to insulin-induced hypoglycemia, the significance of this is less clear because it is an isolated finding.

The limitations of the study relate to its small sample size and observational nature. The size of the cohort may not have enough power to determine true associations. In addition, the precise age and pubertal state of subjects were not available. The directionality of causality between GV and HAAF is unknown and can only be elucidated from interventional studies, in which GV is manipulated by therapy. Such a study would be complex and complicated by concomitant changes in overall glucose and hypoglycemia.

Further studies with larger samples are needed to determine whether GV should be considered prior to intensifying therapy or whether minimization of GV may be useful for preventing and treating HAAF.

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Author Disclosure Statement

N.A. researched data and wrote the manuscript. K.M.D. researched data and wrote the manuscript. No relevant competing interests exist.

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