Revisiting the Relationships Between Measures of Glycemic Control and Hypoglycemia in Continuous Glucose Monitoring Data Sets

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT) identified an inverse relationship between HbA_{1c} and severe hypoglycemia. We investigated the relationship between hypoglycemia and HbA_{1c} in a large type 1 diabetes cohort on multiple daily injection or insulin pump therapy using blinded continuous glucose monitoring (CGM) data. The impact of real-time CGM on these relationships and how these relationships differ with biochemical definitions of hypoglycemia have also been assessed.

RESEARCH DESIGN AND METHODS

CGM data were obtained from the JDRF CGM randomized control trial. Baseline blinded CGM data were used to assess time in hypoglycemia in all individuals. End point data from the CGM intervention group were used to assess the impact of CGM. Percentage of time spent below 3.9, 3.3, 3.0, and 2.8 mmol/L were calculated and quadratic regression plots drawn. Relationships were analyzed visually, and ANOVA was used to assess relationships between glycemia and time below threshold.

RESULTS

J-shaped relationships were observed for all biochemical hypoglycemia thresholds, with the lowest hypoglycemia risk occurring at HbA_{1c} values between 8.1 and 8.6% (65–70 mmol/mol). The use of an average of 5 days/week of CGM flattened the relationships for 3.3, 3.0, and 2.8 mmol/L, and ANOVA confirmed the loss of relationship for the 3.3 mmol/L threshold using CGM.

CONCLUSIONS

The relationship between hypoglycemia and HbA_{1c} in a population with type 1 diabetes is J-shaped. Lower HbA_{1c} values are still associated with increased hypoglycemia risk, although the magnitude of risk depends on biochemical threshold. Real-time CGM may reduce the percentage time spent in hypoglycemia, changing the relationship between HbA_{1c} and hypoglycemia.

The Diabetes Control and Complications Trial (DCCT) study in 1993 (1) demonstrated a substantial reduction in microvascular complication risk in an intensely treated group of adults with type 1 diabetes, and later analysis confirmed a reduction in macrovascular risk (2). However, the intensively treated group had an approximate threefold

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increase in risk of severe hypoglycemia (SH), of which ~60% was attributed to HbA_{1c} (3) with a strong inverse relationship between HbA_{1c} and SH.

Hypoglycemia is the main side effect of exogenous insulin, is associated with physical and psychological morbidity, and impacts on treatment outcomes (4,5). It can be clinically categorized into asymptomatic, symptomatic, and severe, with some discussion around which biochemical threshold defines hypoglycemia in type 1 diabetes (5). The International Hypoglycaemia Study Group has recently recommended a glucose threshold <3.0 mmol/L when reporting hypoglycemia in clinical trials. They also propose 3.9 mmol/L as a glucose alert value (6, 7). Counterregulatory response can occur <3.3 mmol/L in healthy individuals (8), and cognitive dysfunction occurs at <2.8 mmol/L (9). Continuous glucose monitoring (CGM) has enabled more precise definition of hypoglycemia, requiring a minimum duration of 15 min below threshold with events separated by at least 30 min (10).

Since the DCCT, there have been therapeutic and technological advances in diabetes management that reduce hypoglycemia risk independently of glycemic control. The appearance of insulin analogs (11–13), improvements in insulin pump therapy (14), implementation of structured education (15), and multidisciplinary care by specialist teams (16) have all contributed to improvements in type 1 diabetes outcomes, potentially altering the relationships defined in the DCCT. Epidemiological analyses reinvestigating the relationship between SH and HbA_{1c} in pediatric populations have found weak or nonsignificant relationships (17–19). The 30-year follow-up data from the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort demonstrate a reduction in the frequency of SH over time, with the presence of a previous episode of SH the strongest predictor of future episodes of SH (20). Interestingly, the risk of SH in the intensive group was unchanged between the DCCT and EDIC studies above an HbA_{1c} of ~8.5% and in the conventional group was higher in the EDIC cohort above a similar HbA_{1c} threshold, suggesting that the impact of advances in therapies on hypoglycemia has differentially addressed risk in those with lower HbA_{1c} values.

The JDRF CGM study was a 26-week randomized control trial evaluating the efficacy and safety of CGM in children and adults with type 1 diabetes published in 2008 (21–23). It was the first to clearly demonstrate that the continuous use of real-time CGM devices could be associated with improved glycemic control.

We hypothesize that the inverse relationship between HbA_{1c} and SH identified in the DCCT has evolved with advances in treatment and varies with threshold of hypoglycemia. We additionally hypothesize that unblinded CGM has an impact on the interaction between HbA_{1c} and hypoglycemia.

RESEARCH DESIGN AND METHODS

Data Source

Data from the JDRF CGM study (21–23) were used in this analysis. The JDRF data set is freely accessible and was obtained from the Jaeb Center for Health Research (http://diabetes.jaeb.org/Dataset.aspx). All data were analyzed using Stata v14.2 (StataCorp, College Station, TX).

The JDRF CGM study was a 26-week randomized control trial evaluating the efficacy and safety of CGM in children and adults with type 1 diabetes. The study protocol and characteristics of the participants enrolled have been detailed elsewhere (21–23).

Briefly, a total of 448 people with type 1 diabetes treated by multiple-dose injection (MDI) or continuous subcutaneous insulin infusion (CSII) was randomized to CGM (intervention) or capillary glucose monitoring (control). Prior to randomization, all participants underwent 1 week of blinded CGM recording as a baseline for subsequent analysis. Blinded CGM was repeated in the control group at 13 and 26 weeks. HbA_{1c} was assessed at randomization, 13 weeks, and 26 weeks. HbA_{1c} values are reported as DCCT-aligned percentages.

Analysis Design

Relationships between HbA_{1c} and time in hypoglycemia were assessed using baseline blinded data for all participants. A minimum of 6 days of recording was required to be included in the analysis. To assess the impact of CGM, the 26-week HbA_{1c} value and time below threshold for the last 6 weeks of the intervention period were used. Individuals were excluded if there were no CGM data at the beginning or end of this 6 week-analysis. The 26-week HbA_{1c} value and 26-week blinded CGM from the control group were additionally assessed. Again, individuals were excluded if <6 days of CGM data were available. Relationships were analyzed visually using quadratic regression plots, and a relationship between time spent below threshold (3.9, 3.3, 3.0, and 2.8 mmol/L) was assessed across duodeciles of HbA_{1c}. Glycemic variability (GV) measures were analyzed using MATLAB (MathWorks) to discriminate the subgroups with the highest risk of hypoglycemia (24). Episodes of hypoglycemia for CGM reports defined as time spent <3.0 mmol/L for 15 min separated by a minimum of 30 min were also analyzed.

Statistical Analysis

Data were tested for normality and nonparametric tests were used accordingly. Descriptive data are reported as mean (SD) where normally distributed or as median and interquartile range (IQR) where skewed. Quadratic regression models were used to assess relationships between percentage time below threshold and HbA_{1c} for each threshold in each analysis group, and their curves were plotted. Nonparametric ANOVA was used to assess variance of time below threshold across the range of HbA_{1c}. Statistical tests were two-tailed, and the significance level was set at $P < 0.05$.

RESULTS

CGM data were available for 451 individuals at baseline, but 3 individuals were excluded due to missing HbA_{1c} values. Of the 448 individuals included in the baseline analysis (54.9% female, age 25.1 ± 15.8 years, and HbA_{1c} 7.44 ± 0.86%), 231 individuals were assigned to the CGM intervention group and 217 to the control group after the randomization. At 26 weeks, 6-week CGM data were available for 155 individuals in the CGM group after exclusion of 76 individuals due to incomplete data, and CGM data with a minimum of 6 days were available for 185 individuals in the control group after exclusion of 32 individuals due to incomplete data. The baseline clinical characteristics of the individuals included in the analyses at baseline and at 26 weeks are shown in Table 1.

Baseline Data

Quadratic regression curves for the percentage time spent in hypoglycemia below

Table 1—Baseline characteristics for baseline (n = 448), CGM (n = 155), and control (n = 185) groups

	Baseline	CGM	Control
Females, *n* (%)	246 (54.9)	87 (56.1)	106 (57.3)
White race, *n* (%)	423 (94.4)	149 (96.1)	176 (95.1)
Age (years), *n* (%)			
8–14	142 (31.7)	51 (32.9)	51 (27.6)
15–24	141 (31.5)	32 (20.6)	63 (34)
>25	165 (36.8)	72 (46.5)	71 (38.4)
Insulin treatment, *n* (%)			
Pump	365 (81.5)	135 (87.1)	146 (78.9)
Injections	83 (18.5)	20 (12.9)	40 (21.6)
HbA_{1c} (%), *n* (%)			
<7	128 (28.6)	48 (31)	54 (29.2)
7–8.99	301 (67.2)	100 (64.5)	124 (67)
≥9	19 (4.2)	7 (4.5)	8 (4.3)
Diabetes duration in years, median (IQR)	9.4 (5.5, 17.9)	11 (6.2, 22)	9.7 (5.8, 17.9)
Individuals with >1 SH in past 6 months, *n* (%)	38 (8.5)	14 (9)	14 (7.6)

four different biochemical thresholds (2.8, 3.0, 3.3, and 3.9 mmol/L) at different HbA_{1c} values are shown in Fig. 1. J-shaped relationships were observed for each threshold. The highest percentage time below threshold occurs at the lowest HbA_{1c} values. Each curve has an HbA_{1c} value that is associated with the lowest time in hypoglycemia for that threshold, indicated by the curve's nadir point. HbA_{1c} values on either side of this point are associated with progressively increasing hypoglycemia, with the rate of change steeper with decreasing HbA_{1c} values compared with increasing HbA_{1c} values. The regression coefficients, coefficients of determination, and their associated P values were significant for all of the thresholds analyzed ($P < 0.05$ for all of them).

The 3.9 mmol/L curve has the steepest relationship, showing a greater rate of change for a given change in HbA_{1c} at both sides of the nadir, when compared with the 3.3, 3.0, and 2.8 mmol/L curves. J-shaped relationships were also present in the control group at 26 weeks, shown in Fig. 1*C*, confirming the relationships seen at baseline.

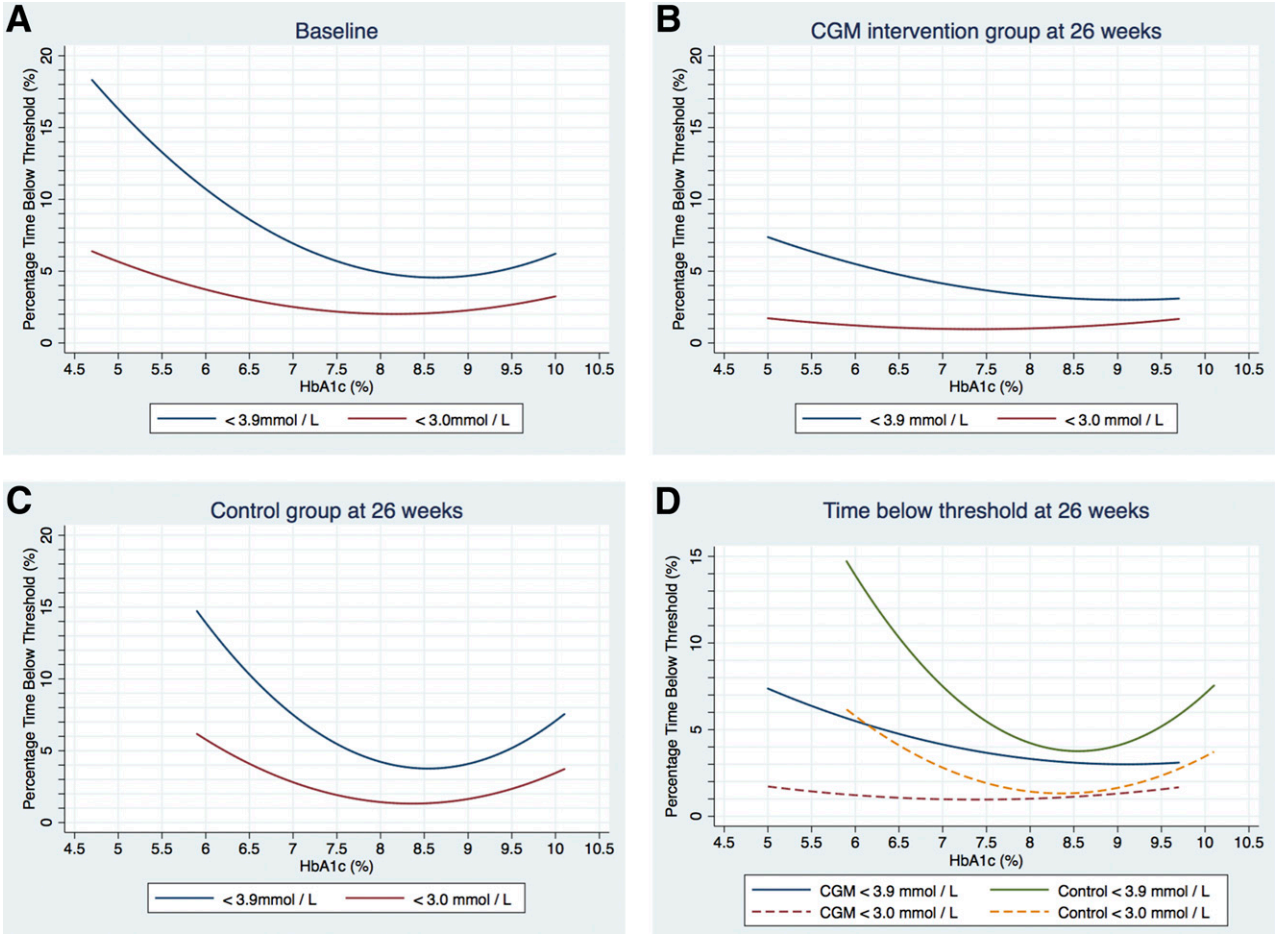

Figure 1—Quadratic regression plots of percentage time in hypoglycemia for each biochemical threshold. *A*: Baseline group (n = 448). *B*: CGM group at 26 weeks (n = 155). *C*: Control group at 26 weeks (n = 185). *D*: Overlap control and intervention groups at 26 weeks.

CGM Group Analysis

CGM changed the nature of the relationships observed in the baseline analysis, as shown in Fig. 1*B*. The overall relationship between time spent <3.9 mmol/L and HbA_{1c} remained significant; however, the slope was shallower at lower and higher HbA_{1c} values. The shapes of the 3.3, 3.0, and 2.8 mmol/L curves changed substantially with unblinded CGM, becoming flattened U-shaped curves with reduced variation in time spent below hypoglycemia threshold with change in HbA_{1c}. The regression curves for time <3.3, <3.0, and <2.8 mmol/L had low R^2 values and were not significant.

The mean percentage of sensor use in our intervention group was 72.5% (5.0 days/week). A total of 59.4% of the subjects used the sensor >70% of the total time during the 6-week CGM analyzed at the end of the follow-up. A total of 13.0% of subjects used the CGM <50% (3.5 days/week) of the time.

The percentage reduction in time spent in hypoglycemia in each HbA_{1c} duodecile has been also calculated using the curves from intervention and control groups at 26-week evaluation. Considering the 3.0 mmol/L as the hypoglycemia cutoff point (in line with the International Hypoglycaemia Study Group), the mean reduction in percentage time in hypoglycemia is 57.6%, with a maximum reduction of 75% of time in hypoglycemia between 6.5 and 7.5% of HbA_{1c}. With 3.9 mmol/L as the hypoglycemia cutoff point, the mean reduction in percentage time in hypoglycemia is 46.3% across the HbA_{1c} range of 6.0–9.5% and the maximum reduction of 43% achieved between HbA_{1c} of 6.0 and 7.5%.

Nadir Point

At baseline, the HbA_{1c} values associated with the lowest time spent below hypoglycemia threshold were 8.1% (65 mmol/mol) for 2.8 mmol/L, 8.2% (66 mmol/mol) for 3.0 mmol/L, 8.4% (68 mmol/mol) for 3.3 mmol/L, and 8.6% (70 mmol/mol) for 3.9 mmol/L. The CGM nadir points for the 2.8, 3.0, and 3.3 mmol/L curves were reduced to 7.3% (56 mmol/mol), 7.4% (57 mmol/mol), and 7.7% (61 mmol/mol), respectively, whereas the nadir point for 3.9 mmol/L increased to 9.1% (76 mmol/mol).

At baseline, the time below threshold hypoglycemia experienced at the National Institute for Health and Care Excellence target HbA_{1c} value of 6.5% (48 mmol/mol) was 8.6% for 3.9 mmol/L, 4.5% for 3.3 mmol/L, 3.0% for 3.0 mmol/L, and 2.5% for 2.8 mmol/L. With CGM, the percentage time below hypoglycemia threshold was 4.8% for 3.9 mmol/L, 1.8% for 3.3 mmol/L, 1.1% for 3.0 mmol/L, and 0.8% for 2.8 mmol/L.

ANOVA

The mean time spent below threshold for each HbA_{1c} duodecile is shown in Fig. 2.

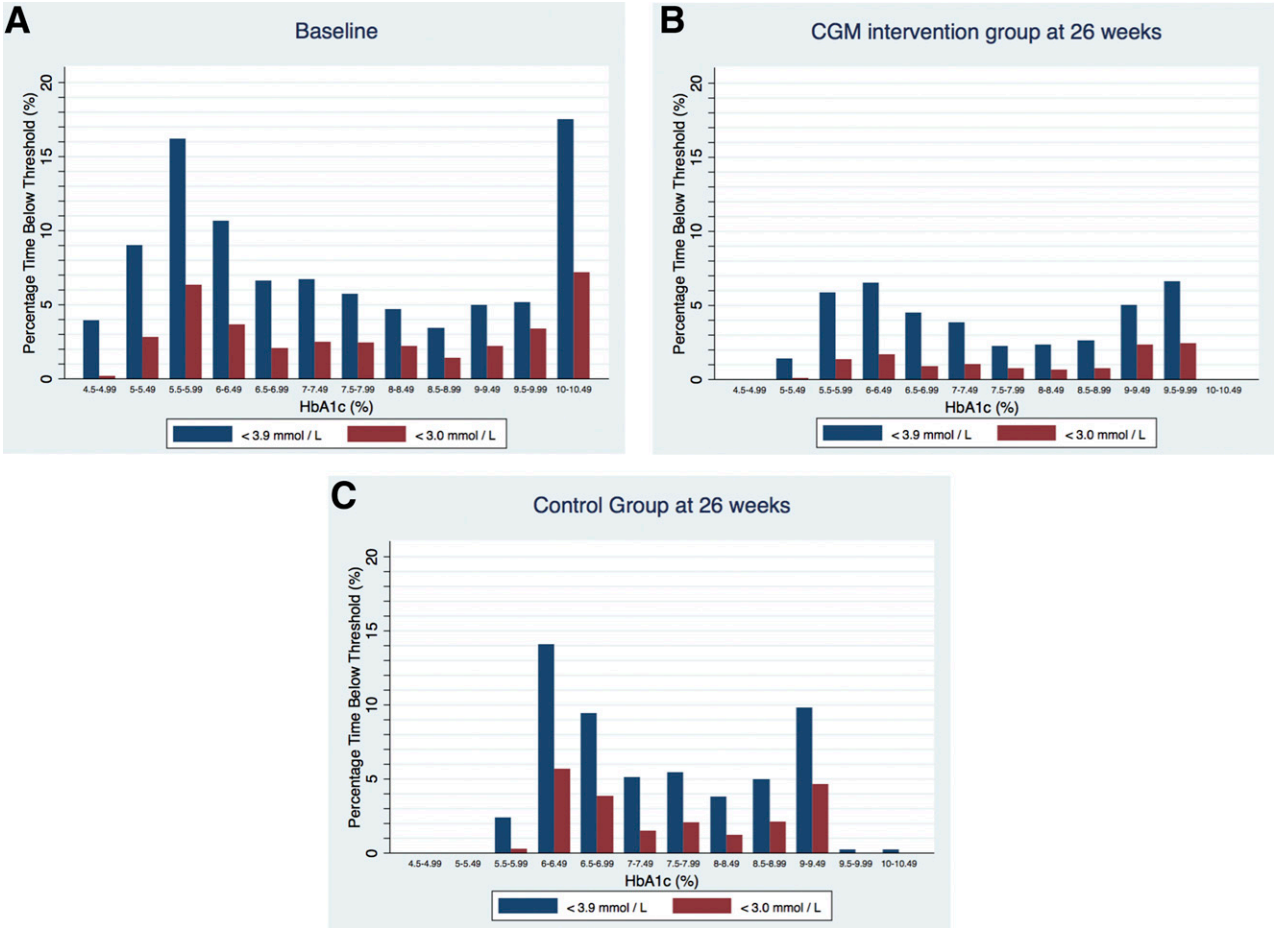

Figure 2—Bar charts showing mean percentage time below threshold (%) at each HbA_{1c} duodecile (%) for each hypoglycemia threshold by analysis group. *A*: Baseline group; *n* = 448. *B*: CGM group at 26-week end point; *n* = 155. *C*: Control group at 26-week end point; *n* = 185. Kruskal-Wallis analysis for Fig. 2 is also included.

At baseline, Kruskal-Wallis analysis identified significant variances for time spent below threshold by HbA_{1c} for time <3.9 ($P < 0.0001$), <3.3 ($P < 0.002$), <3.0 ($P < 0.010$), and <2.8 mmol/L ($P < 0.05$). Significant variance was additionally identified in the control group for 3.9 mmol/L ($P < 0.002$) and 3.3 mmol/L ($P < 0.02$), but not for 3.0 mmol/L and 2.8 mmol/L ($P = 0.09$ and $P = 0.06$, respectively). However, in the CGM group, Kruskal-Wallis analysis only identified significant difference for the 3.9 mmol/L threshold ($P < 0.01$), with no variance of hypoglycemia across HbA_{1c} categories identified for the 3.3, 3.0, or 2.8 mmol/L thresholds (Fig. 2).

GV

Measures of GV were analyzed for each HbA_{1c} duodecile. Kruskal-Wallis analysis identified significant variances by HbA_{1c} for SD and mean amplitude of glucose excursions (MAGE; $P < 0.0001$), with higher values of SD and MAGE occurring with higher duodeciles of HbA_{1c}. Significant variance was also described for low blood glucose index (LBGI), with the lowest duodeciles of HbA_{1c} being associated with a higher LBGI ($P < 0.0001$). However, the coefficient of variation (CV) showed no variance across HbA_{1c} duodeciles ($P = 0.14$).

A post hoc analysis identified three main groups defined by cut points of HbA_{1c} of <6.5% (48 mmol/mol), between 6.5% (48 mmol/mol) and 8.5% (69 mmol/mol), and >8.5% (69 mmol/mol) with significant differences in GV. The analysis was then repeated through the three main groups, and Kruskal-Wallis showed significant variances for SD ($P < 0.0001$), MAGE ($P < 0.0001$), LBGI ($P < 0.0001$), and high blood glucose index (HBGI; $P < 0.0001$). The percentage of CV showed no variance across the groups ($P = 0.06$). In addition, the number of episodes of hypoglycemia was calculated for the three HbA_{1c} groups. Significant variance was identified with an HbA_{1c} of <6.5% (48 mmol/mol) associated with a higher number of hypoglycemia episodes. The results are shown in Table 2.

A multiple linear regression analysis was performed to identify baseline independent factors associated with time <3.0 mmol/L or LBGI >2. The analysis was conducted through the whole cohort and in the group with an HbA_{1c} >8.5% (69 mmol/mol). Age, type 1 diabetes duration, HbA_{1c}, sex, BMI, and type of treatment at baseline (MDI or CSII) were included in the analysis. For time <3.0 mmol/L, the regression showed an R^2 of 0.114 with HbA_{1c}, and treatment modality significantly associated with the time under the threshold. In the analysis of the HbA_{1c} >8.5% group (69 mmol/mol), R^2 was 0.145. For this group, CSII treatment was associated with a reduction in time <3.0 mmol/L by 10% ($P = 0.05$). The analysis showed similar results when LBGI >2 was selected as the dependent variable. Again, higher HbA_{1c} and CSII treatment were significantly associated with lower LBGI across the cohort. For the group with an HbA_{1c} >8.5% (69 mmol/mol), the model showed an R^2 of 0.212, and treatment with CSII was independently associated with a reduction in LBGI of 0.2 ($P < 0.05$).

CONCLUSIONS

Using the largest available CGM data set, we have shown that the relationship between HbA_{1c} and hypoglycemia, defined at any threshold, is J-shaped, with excess time spent below threshold at lower HbA_{1c} values. Furthermore, we have demonstrated that the relationship between HbA_{1c} and hypoglycemia is weakened, and may even be abolished, by CGM and that CGM enables achievement of a lower HbA_{1c} and reduced hypoglycemia risk simultaneously. The increased hypoglycemia risk at higher HbA_{1c} values has been identified in other data sets (19) and is consistent with the persistent risk of SH above an HbA_{1c} of 8.5% (69 mmol/mol) in the DCCT/EDIC follow-up data (20).

From our data, two groups of people are identified at increased risk of hypoglycemia: those with tight glycemic control manifested by a lower HbA_{1c} and reduced glucose variability assessed by SD and MAGE and people with higher HbA_{1c} values and increased glucose variability with higher SD, MAGE, and HBGI values. We hypothesize that this second group is more labile and an important group to recognize, as it is not consistently recognized that people with higher HbA_{1c} values may be at risk for hypoglycemia. This may inhibit access to treatments like CGM that we have shown can address hypoglycemia risk.

Additionally, we have shown that achieving an HbA_{1c} value between 8.1 and 8.6% may be associated with the lowest hypoglycemia risk, and therefore, this may be a safe initial objective for those individuals with a higher HbA_{1c} and a history of severe or challenging hypoglycemia.

Associations between HbA_{1c} and some measures of GV have previously been described in the JDRF data set (25). Furthermore, as demonstrated in the DCCT/EDIC cohort (20), insulin pump use in the JDRF data set was associated with a lower risk of hypoglycemia across the whole range of HbA_{1c}. As 87% of all of the patients included in the JDRF analysis were on a pump, our results cannot be extrapolated to a population solely treated with MDI. Similar analysis using MDI populations would be of interest.

Rates of SH in the JDRF study were low and cannot be assessed by HbA_{1c}, as overall rates were low, and direct comparison

Table 2—Measures of GV through the three main groups of HbA_{1c}

	HbA_{1c} <6.5%	HbA_{1c} 6.5–8.5%	HbA_{1c} >8.5%	*P* value
Mean glucose, mmol/L (mg/dL)	7.3 (132)	9.2 (166)	11.5 (207)	
SD	51.89 (43.60, 63.83)	66.17 (55.92, 76.28)	82.73 (69.81, 96.26)	<0.0001
%CV	39.44 (33.93, 49.30)	39.81 (34.83, 45.37)	39.66 (34.62, 47.19)	0.058
MAGE	105.72 (89.11, 124.60)	130.19 (110.41, 150.88)	160.68 (137.53, 182.74)	<0.0001
LBGI	1.87 (1.13, 4.10)	1.07 (0.43, 2.25)	0.53 (0.18, 1.41)	<0.0001
HBGI	3.87 (2.16, 5.43)	8.29 (5.86, 11.64)	16.30 (12.42, 20.04)	<0.0001
Episodes of hypoglycemia	2 (0, 7.5)	1 (0, 4)	0 (0, 3.5)	<0.05

Data are median (IQR) unless otherwise indicated. Episodes of hypoglycemia are episodes measured by CGM <3.0 mmol/L for at least 15 min separated by at least 30 min.

with SH in the DCCT and EDIC cohorts is not possible. However, CGM has allowed more detailed description of hypoglycemia at differing thresholds and with intervention. Percentage time below hypoglycemic thresholds is a valid measure of hypoglycemia exposure that reduces counterregulatory responses in a dose-response relationship (26), increasing the risk of SH.

CGM Impact on Relationships

CGM abolished the relationship between HbA_{1c} and hypoglycemia <3.3, <3.0, and <2.8 mmol/L, both in the quadratic regression curves and in ANOVA. The relationship between HbA_{1c} and time spent <3.9 mmol/L remained after 26 weeks of CGM, suggesting that mild biochemical hypoglycemia is likely to remain more frequent at the extremes of HbA_{1c} but that it is not more likely to progress to more significant hypoglycemia and may therefore be managed appropriately. This finding has implications for the selection of hypoglycemia thresholds in clinical practice in which, with the support of CGM, 3.9 mmol/L may be considered a safe threshold for action.

The decoupling of the relationship between HbA_{1c} and hypoglycemia that is seen with CGM between the thresholds of 3.9 and 3.3 mmol/L may be explained by the alerts and alarms for hypoglycemia and glucose rate of change. These may be personalized and commonly set between 3.5 and 4 mmol/L, a level that may not prevent glucose values <3.9 mmol/L but may reduce the risk of glucose concentrations <3.3 mmol/L.

Our results further support the role of CGM in enabling and empowering patients to intensify glycemic control without increasing the risk of hypoglycemia. For people achieving the National Institute for Health and Care Excellence target HbA_{1c} of 6.5% (48 mmol/mol) in the JDRF study, at baseline, 64 min/day was spent with glucose <3.3 mmol/L and 36 min/day <2.8 mmol/L. With CGM, these times fell to 26 and 12 min, respectively.

A potential limitation to our study is that the data were derived from early generation CGM devices that are less accurate than contemporary devices, especially in the hypoglycemia range.

Conclusion

We present data that suggest that the relationship between HbA_{1c} and time spent in hypoglycemia in adults and children with type 1 diabetes is J-shaped. Lower HbA_{1c} values remain associated with increased hypoglycemia risk, although the magnitude of risk depends on the biochemical hypoglycemia threshold. Higher HbA_{1c} values are additionally associated with increased hypoglycemia, which may be attributable to greater glucose variability. This has the potential to change the paradigm when deciding suitability of candidates for CGM in terms of clinical benefit. Hypoglycemia risk is minimized at an HbA_{1c} value of ~8.1–8.6% (65–70 mmol/mol) and continuous use of CGM (5 days/week) may reduce the percentage time spent in hypoglycemia, changing the relationship between HbA_{1c} and hypoglycemia for time <3.3 mmol/L while enabling optimization of HbA_{1c}.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.G. and N.O. directed and conducted the statistical analysis, interpreted the data, and wrote the manuscript. A.J.T. conducted statistical analysis, interpreted the results, and wrote the manuscript. M.R. and I.C. contributed to interpreting the results and reviewing the manuscript. V.M. conducted the statistical analysis and contributed to interpreting the results. M.G. and N.O. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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