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BRIEF REPORT

Hypoglycemic Event Frequency and the Effect of Continuous Glucose Monitoring in Adults with Type 1 Diabetes Using Multiple Daily Insulin Injections

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ABSTRACT

Introduction: The benefits of continuous glucose monitoring (CGM) in type 1 diabetes have been established among adults using insulin pumps. The DIAMOND randomized clinical trial examined the effectiveness of using CGM in improving glycemic control in participants using insulin injections. The frequency of hypoglycemic events in this trial has not been previously examined.

Methods: Adults with type 1 diabetes using multiple daily insulin injections (MDI) with A1C values of 7.5% to 9.9% and not using CGM were randomized to adopt CGM (CGM group, $n = 105$) or continue with usual care (control group, $n = 53$). CGM data were collected from both groups at the beginning of the study and after 3 and 6 months. A hypoglycemic event was defined as a series of at least CGM values less than 3.0 mmol/L, separated by 20 min or more, with no intervening values of 3.0 mmol/L or more. Hypoglycemic event rates per 24 h were compared using a linear model adjusted for the baseline event rate per 24 h, baseline A1C, and site as a random effect.

Results: In the CGM group, the median hypoglycemic event rate fell by 30% (0.23 per 24 h at baseline and 0.16 per 24 h at follow-up) while in the control group the rate was nearly unchanged (0.31 per 24 h at baseline and 0.30 per 24 h at follow-up; p value = 0.03).

Conclusion: In the DIAMOND randomized controlled trial, participants in the CGM group experienced a greater reduction in hypoglycemic event rate than participants receiving usual care in the control group.

Trial Registration: Clinicaltrials.gov Identifier: NCT02282397.

Keywords: Continuous glucose monitoring; DIAMOND study; Hypoglycemia; Hypoglycemic event; Multiple daily injection therapy; Type 1 diabetes

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INTRODUCTION

Hypoglycemic events are the main risk of insulin therapy and an important outcome in clinical trials. In the Diabetes Control and Complications Trial, there was a threefold increase in the risk of severe hypoglycemia in the cohort intensively managed attempting to obtain euglycemia [1]. Despite the subsequent increase in use of insulin pumps and insulin analogues, severe and non-severe hypoglycemia

remain problematic for intensive insulin users. In a recent survey of 1317 patients with type 1 diabetes in France [2], a total of 85.3% of respondents reported having at least one hypoglycemic episode in the past 30 days, and there was a mean (SD) of 7.4 (7.4) events per patient-month (or approximately 0.25 events per day).

Although there was past disagreement about how to define and characterize hypoglycemia [3, 4], a recent consensus recommendation from the International Hypoglycaemia Study Group (IHSG) [5] considered serious, clinically important hypoglycemia as glucose concentrations below 3.0 mmol/L. For enumeration of hypoglycemic events established by continuous glucose monitoring (CGM) data, a requirement for 20 consecutive minutes with sensor glucose values below the chosen threshold has been suggested.

Routine use of CGM systems facilitates treatment decisions that can improve glycemic control in people with type 1 diabetes. For adults with type 1 diabetes using multiple daily injections (MDI), the 6-month DIAMOND study [6] established that use of a CGM system was associated with favorable decreases in A1C compared to a control group basing diabetes management decisions on self-monitoring blood glucose alone. In addition to larger decreases in A1C from baseline values compared with the control group, participants randomized to the CGM group had less time with sensor glucose values in various hypoglycemic ranges [less than 3.9 mmol/L (less than 70 mg/dL), less than 3.3 mmol/L (less than 60 mg/dL), and less than 2.8 mmol/L (less than 50 mg/dL)] and a lower area above the curve (AAC) for sensor glucose values below 3.9 mmol/L. Given the favorable reductions in A1C and hypoglycemia AAC, we hypothesized that subjects in the CGM group would also experience a larger reduction in the frequency of hypoglycemic events than the control group.

METHODS

The trial was conducted at 24 endocrinology practices in the USA. Participants had A1C levels ranging from 7.5% to 9.9% at baseline, no recent history of CGM use, and performed blood glucose tests approximately four times per day. Seventeen (11%) of the 158 enrolled participants had experienced at least one episode of severe hypoglycemia in the previous 12 months. All participants were required to complete a 2-week pre-randomization phase by wearing a CGM device for at least 85% of the time to assess compliance and to collect baseline data. Participants were then randomized in a 2:1 ratio to either the CGM group or the control group (basing decisions on blood glucose monitoring results). Participants in the CGM group used the Dexcom G4 Platinum CGM System with software 505 (Dexcom Inc., San Diego, CA). The full protocol and results of the prespecified analyses have been published [6]. A post hoc analysis was performed on data from the DIAMOND study to assess change in

Table 1 Baseline characteristics

	CGM group ($N = 105$)	**Control group ($N = 53$)**
Age (years) mean ± SD	46 ± 14	51 ± 11
Diabetes duration (years), median (IQR)	19 (9–29)	19 (11–35)
Gender—female, *n* (%)	47 (45%)	23 (43%)
Race/ethnicity, *n* (%)		
White non-Hispanic	90 (86%)	42 (79%)
Black non-Hispanic	6 (6%)	3 (6%)
Hispanic or Latino	6 (6%)	8 (15%)
More than one race	2 (2%)	0 (0%)
Unknown/not reported	1 (<1%)	0 (0%)
Weight (kg) mean ± SD	84 ± 20	81 ± 18
A1C (%) mean ± SD	8.6 ± 0.7	8.6 ± 0.6
≥1 severe hypoglycemia reported in the previous 12 months, *n* (%)	8 (8%)	9 (17%)
≥4 injections/day of rapid acting insulin, *n* (%)	34 (32%)	20 (38%)

the frequency of hypoglycemic events, based on the IHSG definition.

Definition of a Hypoglycemic Event

A hypoglycemic event was defined as a series of at least two sensor glucose values less than 3.0 mmol/L (54 mg/dL), lasting at least 20 min, with no intervening values of 3.0 mmol/L or more. The end of a hypoglycemic event was defined as a minimum of 15 consecutive minutes with at least two sensor glucose values of at least 3.0 mmol/L and at least 0.6 mmol/L (10 mg/dL) above the nadir of the event [7]. A new event was temporally separated from any previous event by 15 min or more, with no intervening values less than 3.0 mmol/L.

Statistical Methods

Baseline values correspond to all CGM data available prior to randomization. Follow-up values were obtained during 7-day periods at 12 and 24 weeks (using blinded CGM for the control group and unblinded CGM for the CGM group). Only participants with at least 72 h of CGM data were included in the analysis (two in CGM group and none in control group excluded). The hypoglycemic event rates per 24 h in the two groups were compared using a linear model adjusted for the baseline hypoglycemic event rate per 24 h, baseline A1C, and site as a random effect. As a result of a skewed distribution, the model was based on ranks using van der Waerden scores.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (central commercial institutional board for 17 sites and local boards for the other seven sites) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. Springer's policy concerning informed consent has been followed.

RESULTS

As shown in Table 1, participants in the CGM and control groups were well matched with respect to diabetes duration and A1C. Compared to the CGM group, a higher percentage of participants in the control group had reported

Table 2 Hypoglycemia events lasting at least 20 min at less than 3.0 mmol/L (54 mg/dL) separated by at least 15 min

	CGM group		Control group		p[a]
	Baseline ($N = 105$)	Follow-up ($N = 103$)	Baseline ($N = 53$)	Follow-up ($N = 53$)	
Number of hours of CGM data					
Median (IQR)	314 (305, 320)	315 (298, 326)	316 (309, 322)	298 (279, 316)	
Number of events per 2 weeks					
Median (IQR)	3 (2, 7)	2 (1, 4)	4 (1, 7)	4 (1, 6)	
No events n (%)	10 (10%)	25 (24%)	6 (11%)	9 (17%)	
Event rate per 24 h					
Median (IQR)	0.23 (0.15, 0.46)	0.16 (0.07, 0.30)	0.31 (0.08, 0.54)	0.30 (0.09, 0.46)	
Change in event rate per 24 h					
Median (IQR)		−0.08 (−0.23, +0.07)		0.00 (−0.19, +0.10)	0.03

[a] p value is from a linear model adjusted for the baseline event rate per 24 h, baseline HbA1c, and clinical site as a random effect. As a result of a skewed distribution, the model was based on ranks using van der Waerden scores

severe hypoglycemia (seizure or loss of consciousness) in the previous 12 months. As shown in Table 2, in the CGM group, the median hypoglycemic event rate fell by 30% from 0.23 per 24 h at baseline to 0.16 per 24 h during follow-up, whereas in the control group, the rate was nearly unchanged (0.31 per 24 h at baseline and 0.30 per 24 h at follow-up; p value = 0.03). These rates may not be representative of all adults with type 1 diabetes because of the DIAMOND study's inclusion criteria and the particular criteria used to define a hypoglycemic event.

CONCLUSION

In addition to the beneficial effect of CGM in reducing HbA1c in adult MDI users with type 1 diabetes, this post hoc analysis, using a standard definition for a CGM-defined hypoglycemic event, demonstrates that CGM use compared to blood glucose testing alone is associated with a reduction in the frequency of hypoglycemic events.

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Data Availability. The datasets used in the current study are available from the corresponding author on reasonable request.

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