The use of CGM to identify type 1 diabetic patients with hypoglycemia problems and its impact for avoidance of biochemical hypoglycemia

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ABSTRACT

This cross-over study used a CGM system (DexCom SEVEN PLUS CGM). In a randomized order, participants had either no access (CGM blind) or real time access to current glucose data (CGM open). One objective was to analyze if type 1 diabetic patients with hypoglycemia problems (one episode requiring third party assistance) could be identified by the use of the blinded CGM data. We also analyzed the impact of CGM use on biochemical hypoglycemia. Type 1 diabetic patients with hypoglycemia problems had significant longer diabetes duration (17.0 vs 11.0 yrs.), a higher unawareness score (4.0 vs 2.0) and lower thresholds for detecting hypoglycemia (50.0 vs 65.0 mg/dl) than patients without hypoglycemia problems. During the blinded CGM phase patients with hypoglycemic problems had a significant longer duration of low glucose phases 248 vs. 153 minutes per day (p=.037; <70 mg/dl) respectively 173 vs 96 minutes per day (p=.041; <60 mg/dl). Area under the receiver operating curve (ROC 0.72 p=.03) indicated a sufficient screening performance of the duration of low glucose periods (< 70 mg/dl) for the identification of patients with hypoglycemia problems. A cut-off of 170 minutes per day of time spend in the low glucose range had a sensitivity of 75% and a specificity of 70.3%; the positive predictive value was 52.9%, the negative predictive value was 86.4%. A comparison of blind vs. open CGM showed that time spend in a low glucose range could be significantly more reduced in patients with hypoglycemia problems than in patients without hypoglycemia problems during CGM open (< 60 mg/dl; – 67.8 min per day p=.040; < 50 mg/dl; -50.6 min per day, p=.038; < 40 mg/dl; -41.4 min. per day, p=.03). This study shows that CGM has an unused potential for identifying type 1 diabetic patients at risk for hypoglycemia problems in clinical practice as well as for avoidance of biochemical hypoglycemia, which plays a pivotal role for the development of hypoglycemia associated autonomic failure.

INTRODUCTION

The potential of CGM for the identification of patients with hypoglycemia problems and for the avoidance of hypoglycemic episodes is not sufficiently understood. This is partly due to the fact that most CGM studies are powered to detect an improvement in glycemic control as primary outcome. Besides, patients with hypoglycemia problems are often excluded from study participation. This short term pilot study aimed at two objectives:

1. to analyze whether CGM data can be used to identify people with type 1 diabetes and hypoglycemia problems
2. to analyze whether people with type 1 diabetes and hypoglycemia problems had more benefit from CGM use than people with type 1 diabetes but without hypoglycemia problems with regard to the duration of biochemical hypoglycemia

METHODS

This cross-over study used the DexCom SEVEN PLUS CGM system. In a randomized order participants had either no access (CGM blind) or real time access to current glucose data (CGM open) and were alerted if glucose fell beneath a lower limit of 80 mg/dl. Each of the CGM phases was scheduled for 96 to 120 hours. In this study type 1 diabetes patients with and without hypoglycemia problems were included. Hypoglycemia problems were defined as having experienced at least one hypoglycemic episode requiring third party assistance for recovery during the past year. Patients also completed the hypoglycemia awareness scale (Clarke et al, Diabetes Care, 18, 1995, 517-522).

RESULTS

In this study 40 people with type 1 diabetes took part.

- Sample characteristics are depicted in table 1. People with hypoglycemia problems had significant longer diabetes duration, a higher unawareness score and reported a significant lower threshold for recognizing hypoglycemia symptoms. Thus, clinical characteristics of people with hypoglycemia problems showed expected differences to people without hypoglycemia problems (table 1).
- In the CGM blind-phase, the wearing time of the sensor was 109 hours. The accuracy of the system was in the expectable accuracy range for CGM. Median glucose levels showed a moderate overall hyperglycemia, which fits to the duration of eu- and hyperglycemic phases. There was no significant difference between people with and without hypoglycemia problems with regard to the variables mentioned above (table 2).
- During the CGM blind-phase, CGM-data showed that people with hypoglycemia problems spent a significant longer time in the low glucose range than people with type 1 diabetes without hypoglycemia problems (figure 1).
- The duration spent in the hypoglycemic glucose range can be used to identify people with type 1 diabetes and hypoglycemia problems. The Receiver Operating Characteristics Curve showed a significant better “screening performance” of the duration of low glucose phases for the identification of people with hypoglycemia problems than a random chance classification. Optical inspection of the ROC suggests a cut-off point of 170 minutes spent in a hypoglycemic glucose range (< 70 mg/dl) to identify people with hypoglycemia problems with an optimal sensitivity (75%) and specificity (70.3%). The positive predictive value of 52.9% suggests that every second patient with a duration of hypoglycemic phases by 170 minutes or more has hypoglycemia problems (Figure 2).
- In figure 3 the reduction of time spent in the hypoglycemic range during the CGM open-phase compared to CGM blind-phase is shown. People with hypoglycemia problems could reduce their time spent in the hypoglycemic range significantly more than people without hypoglycemia problems.
- The effect sizes for hypoglycemia avoidance in people with diabetes are depicted in figure 4. The effect sizes suggest a moderate to large effect of CGM use for avoiding biochemical hypoglycemia in people with hypoglycemia problems.

CONCLUSION

This pilot study showed that CGM has an unused potential for identifying type 1 diabetic patients at risk for hypoglycemia problems in clinical practice. Hypoglycemia associated autonomic failure (Haaf), exposing patients to more frequent and longer phases of hypoglycemia, has emerged as a key factor for the development of hypoglycemia problems in people with diabetes. People with type 1 diabetes and hypoglycemia problems can be identified with satisfactory precision by using CGM. Furthermore, open CGM provides current glucose levels and alerts people with diabetes if pre-defined hypoglycemic glucose limits are met. These preliminary data suggest that CGM allows people with hypoglycemic problems to reduce exposure to hypoglycemic glucose values more effectively than people without hypoglycemia problems. The observed effect sizes are rather large. The obvious limitation of this study is its small sample size and short duration. Therefore, trials with larger samples and longer duration are necessary to demonstrate the ability of CGM to reduce exposure to hypoglycemia - a key risk factor for Haaf - in people with type 1 diabetes and hypoglycemia problems.

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Table 1: Sample characteristics of the total sample and for people with and without hypoglycemia problems. Depicted are median and Inter-Quartil-Range (IQR)

Parameter	All (N=40)	Without hypoglycaemia problems (N=28)	With hypoglycaemia problems (N=12)	p
% female (n)	22.5 (9)	28.6 (8)	8,3 (1)	.160
Age yrs.	44.5 (34.5 ; 48.0)	43.5 (31.5 ; 47.0)	46.0 (37.0 ; 49.0)	.383
Diabetes duration yrs.	13.5 (7.0 ; 22.5)	11.0 (5.0 ; 19.5)	17.0 (14.0 ; 24.5)	.045
A1c %	8.0 (7.2 ; 9.1)	8.1 (7.4 ; 9.3)	7.6 (7.0 ; 8.0)	.074
Hypoglycemia-unawareness Score	2.0 (1.0 ; 3.7)	2.0 (1.0 ; 2.0)	4.0 (2.0 ; 4.3)	.001
Glycemic threshold for symptomatic hypoglycemia mg/dl	60.0 (50.0 ; 70.0)	65.0 (59.7 ; 70.0)	50.0 (45.0 ; 60.0)	.002

Table 2: Results of CGM blind-phase of the total sample and for people with and without hypoglycemia problems. Depicted are median and IQR

Parameter	All (N=40)	Without hypoglycaemia problems (N=28)	With hypoglycaemia problems (N=12)	p
CGM use hours	109.8 (102.3 ; 114.4)	108.8 (102.0 ; 114.0)	112.6 (105.5 ; 115.1)	.386
Median relative absolute difference (MARD)	16,8 ±4,7	16,6% ±5	17.5 ±4	.539
Glucose level mg/dl	137.0 (123.1 ; 153.8)	137.8 (126.9 ; 154.5)	128.8 (114.2 ; 146.2)	.166
Duration of hyperglycemic phases (>180 mg/dl) per day (minutes)	231.5 (171.5 ; 352.0)	239.5 (199.0 ; 352.0)	219.0 (95.0 ; 366.5)	.571
Duration of euglycemic phases (>70 to ≤180 mg/dl) per day (minutes)	873.0 (690.5 ; 1006.5)	873.0 (707.0 ; 947.0)	905.0 (639.5 ; 1010.0)	.918

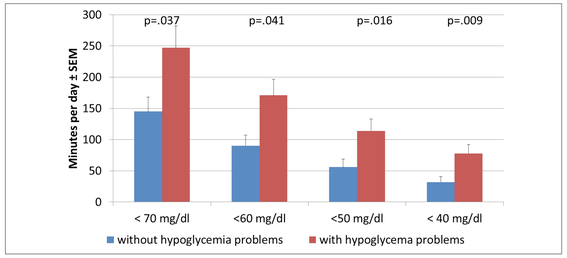

Figure 1: Mean duration of hypoglycemic phases per day in people with and without hypoglycemia problems ± SEM adjusted for order effects

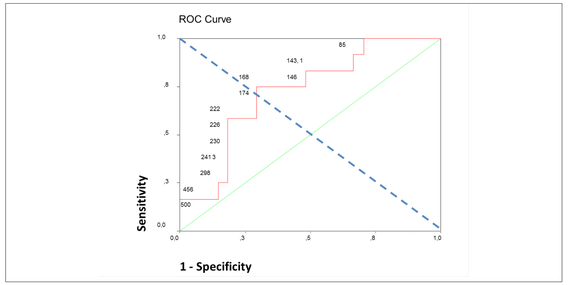

Figure 2: Area under the receiver operating characteristics curve for identification of people with diabetes and hypoglycemia problems (Area under ROC .72, p=03)

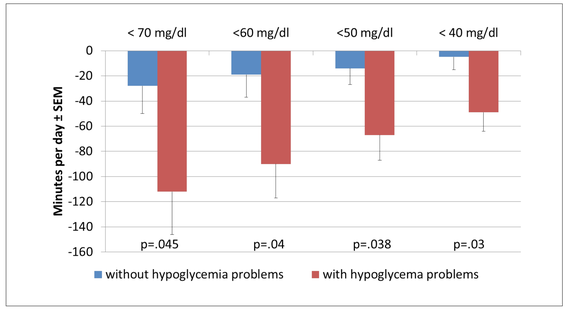

Figure 3: Mean change in the duration of hypoglycemic phases per day in people with and without hypoglycemia problems ± SEM adjusted for order effects

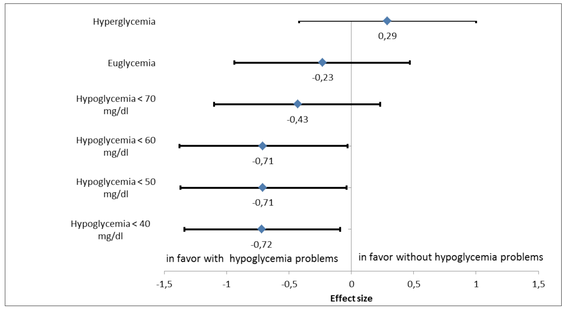

Figure 4: Effect sizes of CGM use for avoidance of hypoglycemia in people with and and without hypoglycemia ± 95% CI