People with Type 1 Diabetes and Increased Hypoglycemia Frequency have a Higher Risk for Nocturnal Hypoglycemia During the Second Half of the Night

Guido Freckmann[1], Peter Wintergerst[1], Dominic Ehrmann[2], Norbert Hermanns[2], Gabriele Faber-Heinemann[3], Lutz Heinemann[3]

[1]Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany

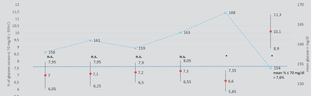
[2]FIDAM - Research Institute Diabetes Academy, Diabetes Center Mergentheim, Bad Mergentheim, Germany, [3]Science-Consulting in Diabetes GmbH, Duesseldorf, Germany

https://doi.org/10.20378/irbo-52412

ABSTRACT

Based on the baseline data of a multi-center randomized CGM trial (HypoDE), we analyzed the glucose recordings of participants with an increased hypoglycemia frequency. All 126 participants had type 1 diabetes and were on an MDI insulin therapy (age 46.5±11.5 yrs., 36.5% female, HbA1c 7.5±1.0%, hypoglycemia unawareness score 5.0±1.1). Each participant used a blinded CGM system (DexCom Gen 4) for 28 days. The percentage of glucose readings ≤70 mg/dl over a 24h period (6 am to 10 am; 10 am to 2 pm, 2 pm to 6 pm, 6 pm to 10 pm, 10 pm to 2 am, and 2 am to 6 am) were analyzed. During the whole day, on average 7.6% of all 288 glucose readings per patients were ≤70 mg/dl. From morning to evening, 192 of ≤70 mg/dl readings were between 7.0% and 7.3%. In the early night, this percentage was lower than during the late night, in which the percentage of ≤70 mg/dl values rose to >10% (p<0.001). A similar pattern could be observed for mean glucose values during these intervals (figure).

Since study participants were at higher risk for hypoglycemia, they appear to have an elevated bedtime glucose in order to avoid nocturnal hypoglycemia. This worked well during the first half of the night; however, during the second half of the night the hypoglycemia risk increased considerably. A modification of nocturnal basal insulin supply should be considered in this high risk group.



BACKGROUND

Nocturnal hypoglycemia is a challenge for people with diabetes and reduced hypoglycemia awareness. We examined the frequency of hypoglycemic glucose readings during night time, by using continuous glucose monitoring (CGM) in participants of a multi-center randomized trial (HypoDE). The HypoDE study is a CGM trial conducted in specialized diabetological outpatient clinics in Germany with type 1 diabetic patients, who have an elevated risk of hypoglycemia and are on a multiple daily insulin injections therapy (MDI). Specifically, we analyzed if hypoglycemic glucose readings occurred preferably during early (10:00 pm to 02:00 am) or late night (02:00 am to 06:00 am). In a second step, we analyzed if treatment factors, hypoglycemia unawareness, glycemic control or demographic factors were associated with the risk of nocturnal low glucose readings.

METHODS

We analyzed baseline data of 126 participants of the HypoDE study. Each participant used a blinded CGM system (Dexcom G4) for 28 days. The mean sensor glucose and the percentage of glucose readings ≤70 mg/dl and ≤55 mg/dl during different times of a day (6 am to 10 am; 10 am to 2 pm, 2 pm to 6 pm, 6 pm to 10 pm, 10 pm to 2 am, and 2 am to 6 am) were analyzed. Participants also completed a Hypoglycemia Unawareness Questionnaire (Scale range from 0 = maximum hypoglycemia awareness to 7 = maximum hypoglycemia unawareness). Questionnaire authors suggest a cut-off score of 4 to define hypoglycemia unawareness (Clarke et al. Diabetes Care, 1995, 18(4):517-522). In a second analyses step univariate and multivariate associations (stepwise logistic regression analysis) between late night hypoglycemic readings and treatment factors, history of hypoglycemia as well as medical or demographic variables were analyzed.

RESULTS

- Sample characteristics are described in table 1. Participants had a rather long diabetes duration and a rather good glycemic control as indicated by a mean A1c of 7.5%. Many participants had experienced severe hypoglycemic events during the past 12 months and asymptomatic mild hypoglycemia was also reported by most of the patients. There was a high prevalence of hypoglycemia unawareness in this sample as indicated by the mean score of the hypoglycemia unawareness questionnaire.
- The key CGM outcomes are reported in table 2. Mean wearing time of the blinded CGM device was 26.8 days. Mean sensor glucose correspondents to A1C. Overall 7.6 % of all glucose readings were indicating mild hypoglycemia (≤ 70 mg/dl) and 3.3 % indicated more advanced hypoglycemia (≤ 55 mg/dl).
- The mild and moderate hypoglycemia readings during different times of the day are depicted in figures 1 and 2. Both figures show that mild and moderate hypoglycemia occurred preferably during late night between 02:00 am and 06:00 am. Percentage of mild and advanced hypoglycemia were below the average percentage of the whole day during the early night (10:00 pm to 02:00 am). Quantile plots in figure 3 also indicate that the distribution of mild and advanced hypoglycemic glucose readings during late night can be clearly discriminated from the distribution of these readings during other times of the day.
- The mean glucose during late night was also significant lower than the average glucose level, whereas the mean glucose during the early night was significantly higher than the average glucose level (figure 4).
- Univariate analyses showed that advanced hypoglycemia during the late night was not associated with treatment factors except the use of analog prandial insulin (figure 5), but with the total hypoglycemia unawareness score and previous mild or severe hypoglycemia (figure 6). Low mean sensor glucose and A1c as well as long diabetes duration were associated with percentage of advanced hypoglycemic glucose readings (figure 7).
- A multivariate step-wise logistic regression analysis with advanced hypoglycemic glucose readings as dependent variable (none in 22 participants, and 103 in participants with advanced hypoglycemia glucose readings) showed that previous severe hypoglycemia and frequent asymptomatic biochemical hypoglycemia were associated with a 8.35-fold respectively 8.94-fold increase for the risk of late night hypoglycemia, whereas the increase of mean sensor glucose per 27 mg/dl lowered the risk by 58% (figure 8).

CONCLUSION

Nocturnal hypoglycemia was more frequent during the second half of the night. Since mean glucose values were significantly higher during the early night than the average glucose levels, it appears that participants might have elevated their bedtime glucose to avoid nocturnal hypoglycemia. This worked well during the first half of the night; however, during the second half of the night the hypoglycemia risk increased considerably. Multivariate analysis suggests that in this group insulin treatment was not associated with the risk of advanced hypoglycemia during the late night. Instead, hypoglycemia unawareness and the mean glucose level were associated with late night hypoglycemia. This suggests that reduction of hypoglycemia unawareness might be important to reduce nocturnal hypoglycemia as well. In addition, technical solutions like CGM-based hypoglycemia alerts might be also able to reduce nocturnal hypoglycemia without compromising glycemic control.

Table 1: Sample characteristics

Sample characteristics (n=126)	Mean (±SD) or %
Age (±SD) in yrs.	46.5 (±11.6)
% female	36.5 %
Diabetes duration (±SD) in yrs.	20.5 (±13.7)
A1c (±SD) in %	7.5 (±1.0)
Hypoglycemia unawareness score (±SD)	5.0 (±1.1)
% with frequent asymptomatic hypoglycemia	73.0 %
% with severe hypoglycemia (third party assistance)	56.0 %
% with severe hypoglycemia (coma seizure)	29.4 %
% with basal analog insulin	96.8 %
% with 1 basal insulin injection	56.0 %
% with prandial analog insulin	86.5 %
Daily insulin dose (± SD) in IU/KG	0.58 (±0.25)

Table 2: CGM characteristics

CGM characteristics (n=126)	Mean (±SD)	Median (IQR)
CGM wearing time in days	26.8 (±4.3)	27.2 (26.2 – 27.6)
Sensor glucose in mg/dl	161 (±27.9)	157 (138 – 181)
% of glucose readings ≤ 55 mg/dl	3.3% (±3.7%)	2.1% (0.1% – 4.5%)
% of glucose readings ≤ 70 mg/dl	7.6% (±6.4%)	5.9% (3.0% – 11.4%)
% of glucose readings > 70 to ≤ 180 mg/dl	57.6% (±14.6%)	56.9% (47.6% – 66.6%)
% of glucose readings > 180 mg/dl	34.8% (±16.6%)	33.4% (22.4% – 46.4%)

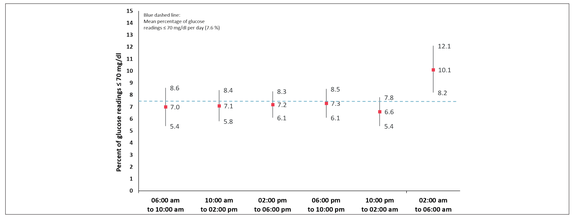


Figure 1: Percentage of glucose readings ≤ 70 mg/dl (± 95% confidence interval) depending on time of the day

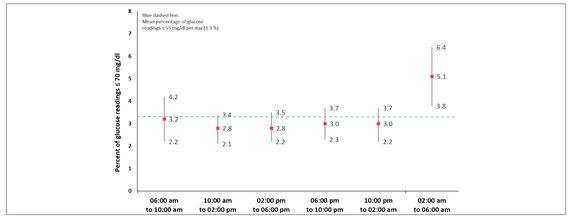


Figure 2: Percentage of glucose readings ≤ 55 mg/dl (± 95% confidence interval) depending on time of the day

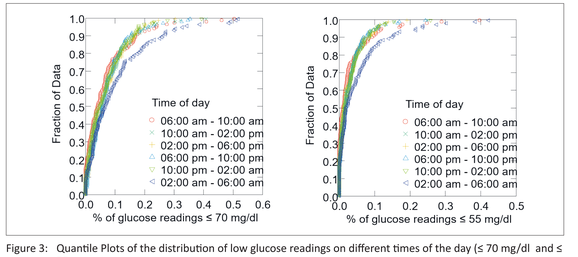


Figure 3: Quantile Plots of the distribution of low glucose readings on different times of the day (≤ 70 mg/dl and ≤ 55 mg/dl)

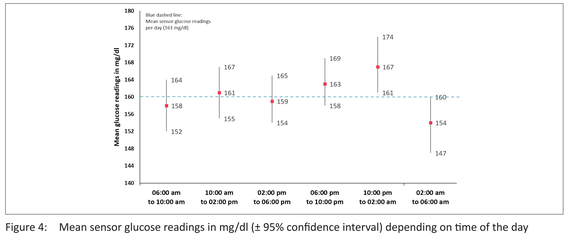


Figure 4: Mean sensor glucose readings in mg/dl (± 95% confidence interval) depending on time of the day

Contact Information

Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm
Guido Freckmann
Ulm, Germany
Phone: 0049 731 509900, Email: guido.freckmann@idt-ulm.de

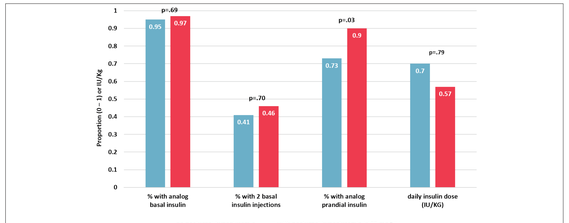


Figure 5: Difference between participants with and without late night glucose readings ≤ 55 mg/dl regarding treatment factors (use of analog prandial or basal insulin, number of basal insulin injections and daily insulin dose)

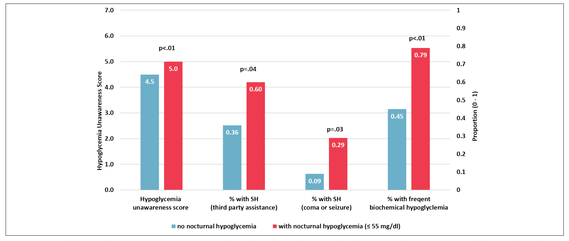


Figure 6: Difference between participants with and without late night glucose readings ≤ 55 mg/dl regarding hypoglycemia unawareness score and the occurrence of mild or severe hypoglycemia

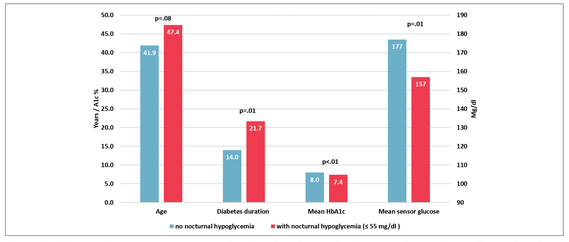


Figure 7: Difference between participants with and without late night glucose readings ≤ 55 mg/dl regarding demographic factors (age or diabetes duration) and indicators of glycemic control (A1c and mean sensor glucose)

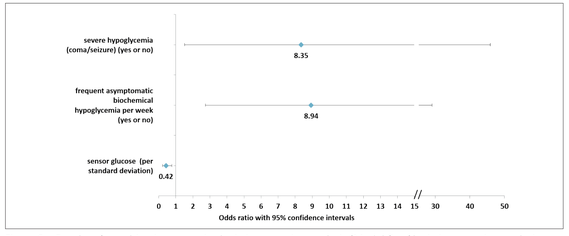


Figure 8: Results of a multivariate stepwise logistic regression analysis (Model fit of logistic regression analysis expressed as Nagelkerke R^2 = 0.35)