# Clinical and Psychological Characteristics of People with Type 1 Diabetes and a High Risk of Hypoglycemic Events

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

[1] Science-Consulting in Diabetes GmbH, Duesseldorf, Germany, [2]Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany

[3]FIDAM - Research Institute Diabetes Academy, Diabetes Center Mergentheim, Bad Mergentheim, Germany

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## ABSTRACT

For the HypoDE study people with type 1 diabetes treated by MDI with a high risk of hypoglycemic events were recruited. Baseline data of 126 study participants were analyzed (age 46.5±11.6 yrs., 36.5% female, HbA1c 7.5±1.0%). They reported 4.5±9.2 episodes of severe hypoglycemia per year (third party assistance for recovery required) and 1.0±2.4 episodes of hypoglycemic episodes with coma or seizure per year prior to study participation. This corresponds to 700%, respectively 600% more hypoglycemic episodes than observed in the DCCT (0.64, respectively 0.16 episodes per year). Blinded CGM recordings for 28 days during the run-in phase of the study revealed that the participants had 12.7±11.8 hypoglycemic events per 28 days (= glucose reading ≤55 mg/dl for at least 20 min). They spent 109 min per day at glucose levels ≤70 mg/dl and 34 min per day ≤50 mg/dl. This corresponds to 32.5%, respectively 55% more time in this range that the adult participants in the JDRF CGM-trial. The hypoglycemia unawareness score of the participants was 5.0±1.1 (out of a maximum score of 7); 95.2% yielded a score ≥4, which is used as a cut-off score for hypoglycemia unawareness. In the Hypoglycemia Fear Survey, HypoDE participants achieved a score of 32.3±15.5 and a Diabetes Distress Scale mean item score of 2.5±1.2. Both scores were higher than those which could be expected in a sample of people with type 1 diabetes, not specifically selected by hypoglycemia problems.

In summary, these data suggest that HypoDE participants represent patients with a high risk of clinical as well as biochemical hypoglycemic events. Compared to the "typical" patient with type 1 diabetes, these subjects reported a high amount of hypoglycemia worries and diabetes-related distress.

## BACKGROUND

For the HypoDE study people with type 1 diabetes treated by MDI with a high risk of hypoglycemic events were recruited. In this study, we put the CGM profiles of participants of the HypoDE into the context of other CGM landmark studies (DIAMOND[1], GOLD[2], IN CONTROL[3], JDRF adult sample[4], Battelino et al. CGM-hypoglycemia trial[5] and Battelino et al. CGM-CSII trial[6]). We also compared psychosocial characteristics of this sample regarding diabetes distress and fear of hypoglycemia with the normative samples used for the psychometric evaluation of the Diabetes Distress Scale[7] and the Hypoglycemia Fear Survey[8].

## METHODS

We analyzed baseline data of 126 participants of the HypoDE study, a CGM trial which is conducted in specialized diabetological outpatient clinics in Germany. All participants had type 1 diabetes and were on MDI Treatment. Key inclusion criterion was impaired hypoglycemia awareness or experience of a severe episode of hypoglycemia (third party assistance needed for recovery or coma or seizure). At baseline, each participant used a blinded CGM system (Dexcom G4) for 28 days. We determined the CGM profile by calculating percentage and duration of time spent in different glucose ranges (≤ 50 mg/dl, ≤ 55 mg/dl, ≤ 70 mg/dl, 71 -180 mg/dl and > 180 mg/dl). We compared these CGM profiles with those of the above mentioned CGM landmark studies. We standardized the CGM profiles by setting the respective HypoDE parameter at 100%, thus a lower than 100% result in one of the CGM studies indicated a lower value of this parameter and a higher than 100% result indicated a higher value of this parameter than in the HypoDE study. HypoDE participants also completed the Diabetes Distress Scale for type 1 diabetes (DDS) and the Hypoglycemia Fear Survey II (HFS). We compared the results of the HypoDE participants with the results of the normative samples, which were used for the psychometric evaluation of these scales.

## RESULTS

- Baseline data of 126 study participants are described in table 1. There was a long diabetes duration, nearly all participants reported reduced hypoglycemia awareness. They reported 4.5 ±9.2 episodes of severe hypoglycemia with the need of third party assistance for recovery per year and 1.0 ±2.4 episodes of severe hypoglycemic episodes with coma or seizure per year prior to study participation. This corresponds to 700%, respectively 625% more severe hypoglycemic episodes than observed in the DCCT (0.64, respectively 0.16 episodes per year). Baseline results indicated a high prevalence of clinical significant hypoglycemia problems. Participants reported also rather high levels of diabetes distress and hypoglycemia worries.
- The key outcomes of blinded CGM recordings during the 28 days baseline phase of the HypoDE study are shown in table 2.
- Key hypoglycemia-related inclusion/exclusion criteria or hypoglycemia-related primary outcomes in the CGM landmark studies are described in table 3. Only one study used hypoglycemia problems (Battelino et al. CGM-CSII trial) as an exclusion criterion. There were only two studies (IN CONTROL and HypoDE), which specifically selected participants with hypoglycemia problems. The Battelino et al. CGM-hypoglycemia trial (although not including specifically participants with hypoglycemia problems) and the HypoDE study had a hypoglycemia-related primary outcome. The IN CONTROL study selected participants with hypoglycemia-problems, but used time in range as primary outcome, which is only partially hypoglycemia related, since time in range can also be increased by avoidance of hypoglycemia. There are three studies (DIAMOND, GOLD and HypoDE) which exclusively included participants with MDI, but only the HypoDE hat a hypoglycemia-related primary outcome.
- In figure 1 the time spent in or percentage or duration of mild and moderate hypoglycemia (≤ 70 mg/dl; ≤ 55 mg/dl; ≤ 50 mg/dl) is shown. JDRF reported duration of time ≤ 50 mg/dl and GOLD reported percentage of glucose values < 54 mg/dl. Participants of the HypoDE study had more or longer mild to moderate hypoglycemia than participants of most other CGM studies, only participants of the IN CONTROL study spent more time in glucose range ≤ 70 mg/dl.
- In figure 2 the percentage or duration of time in the euglycemic range (>70 mg/dl to ≤ 180 mg/dl) and in hyperglycemia (> 180 mg/dl) is shown. Participants of GOLD and DIAMOND experienced less time in euglycemic range and more hyperglycemia. The HypoDE sample has comparable time in range with the JDRF and IN CONTROL study.
- In figure 3 the comparison between the HypoDE sample and the normative samples used for psychometric validation of HFS II are depicted. Participants of the HypoDE sample described more worries about hypoglycemia than the total normative sample and the subsample not selected because of hypoglycemia problems. There were equivalent worries about hypoglycemia in the HypoDE sample and in a subsample of the normative sample, which was selected because of hypoglycemia problems. The HFS behavior/avoidance scale yielded comparable results.
- In figure 4 the DDS total score and DDS subscales are shown in the HypoDE sample and in the normative sample used for the psychometric validation of the DDS for people with type 1 diabetes. Participants of the HypoDE had a higher DDS total score and reported more hypoglycemia distress and more family-related distress than in the normative sample of the DDS.

## DISCUSSION

Comparison of CGM profiles of the HypoDE study indicated that this sample has more biochemical hypoglycemia than most samples of other CGM landmark studies. This might be partially due to inclusion/exclusion criteria and treatment factors. Participants of the IN CONTROL study showed more expose to biochemical hypoglycemia. However, the IN CONTROL sample was smaller and had a 10 year longer diabetes duration than the HypoDE sample. The later might indicate a more advanced diabetes disease. Patient reported outcomes indicate that more exposure to hypoglycemia corresponds with more worries about hypoglycemia and more diabetes-related distress. A limitation of this comparison is an obvious lack of consensus what parameters of the CGM profile are reported respectively about the choice of descriptive statistics.

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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) |
| % Hypoglycemia Unawareness (Unawareness Score ≥ 4) | 95.2 % |
| % with severe hypoglycemia (third party assistance) | 56.0 % |
| # of severe hypoglycemia per year (third party assistance) | 4.5 (±1.1) |
| # of severe hypoglycemia per year (coma, seizure) | 1.0 (±2.4) |
| Diabetes Distress Scale total score (±SD) | 2.5 (±0.8) |
| HFS II - Worry Score (±SD) | 32.3 (±15.5) |
| HFS II - Behavior/Avoidance Score (±SD) | 20.8 (±9.0) |
| Mean 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 ≤ 50 mg/dl | 2.4% (±3.0%) | 1.3% (0.5% – 3.1%) |
| % 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%) |
| Duration of time spent in hypoglycemic range (≤ 50 mg/dl) per day in minutes | 34.1 (±42.6) | 19.7 (7.0 – 45.3) |
| Duration of time spent in hypoglycemic range (≤ 55 mg/dl) per day in minutes | 47.9 (±53.4) | 30.0 (10.9 – 66.2) |
| Duration of time spent in hypoglycemic range (≤ 70 mg/dl) per day in minutes | 109.0 (±91.4) | 83.0 (44.4 – 165.7) |
| Duration of time spent in euglycemic range (> 70 - ≤ 180 mg/dl) per day in minutes | 828.5 (±209.9) | 818 (683.4 – 957.5) |
| Duration of time spent in hyperglycemic range (> 180 mg/dl) per day in minutes | 502.5 (±239.2) | 483.6 (323.6 – 666.4) |

Table 3: Key hypoglycemia-related inclusion / exclusion criteria or hypoglycemia-related primary outcomes in the CGM landmark studies

| Study | Hypoglycemia as exclusion criterion | Hypoglycemia as inclusion criterion | Primary endpoint specifically related to hypoglycemia | % with MDI |
|---|---|---|---|---|
| HypoDE | No | Yes | Yes: number of hypoglycemic events | 100% |
| JDRF adults | No | No | No: A1c | 16% |
| Battelino (CSII) | Yes | No | No: A1c | 0% |
| Battelino (Hypo) | No | No | Yes: time spent in hypoglycemia | 41% |
| IN CONTROL | No | Yes | Partially: Time spent in range | 56% |
| DIAMOND | No | No | No: A1c | 100% |
| GOLD | No | No | No: A1c | 100% |

### Contact Information

Science Consulting in Diabetes GmbH
**Prof. Dr. Lutz Heinemann**
Kehler Str. 24, 40468 Duesseldorf, Germany
L.heinemann@science-co.com

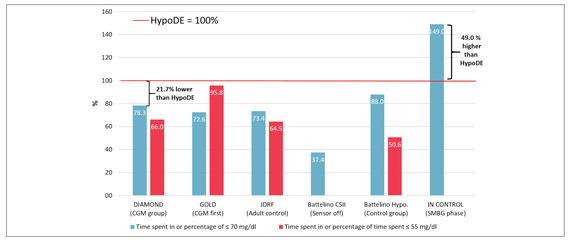


Figure 1: Time spent in or percentage of mild (≤ 70 mg/dl) to moderate (≤ 55 mg/dl) hypoglycemia per day (JDRF and DIAMOND ≤ 50 mg/dl, Gold < 54 mg/dl) during baseline or run-in visit (compared to HypoDE)

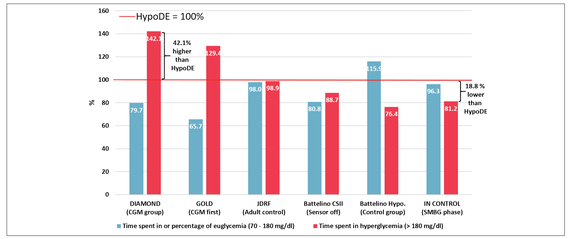


Figure 2: Time spent in euglycemic (> 70 mg/dl and ≤ 180 mg/dl) and hyperglycemic (> 180 mg/dl) range per day compared to HypoDE

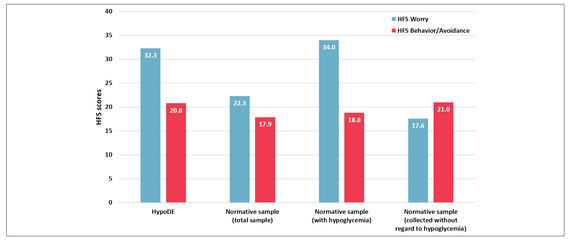


Figure 3: Comparison of HFS scores in HypoDE with the normative samples of the Hypoglycemia Fear Survey II

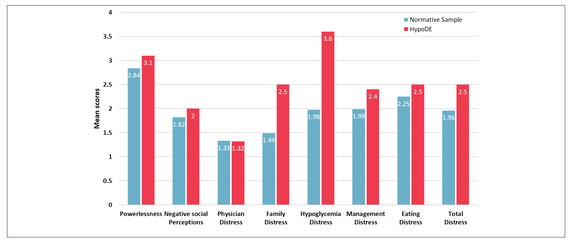


Figure 4: Comparison of the DDS-total and the DDS-subscale scores in HypoDE and the normative sample of the Diabetes Distress Scale