Occurrence of severe hypoglycaemic events in the future: Analysis of CGM data of the HypoDE study

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BACKGROUND AND AIMS

Hypoglycaemia is still the limiting factor of a normoglycaemic-oriented insulin therapy in diabetes. Frequent and/or long lasting mild hypoglycaemic episodes are risk factors for the development of hypoglycaemia problems with an enhanced risk for severe hypoglycaemia. rtCGM can assess and reliably quantify exposure to low glucose values and therefore allows an estimation of hypoglycaemia risk. Thus, the international consensus statement on CGM data defined CGM-derived risk markers for hypoglycaemia[1].

However, more empirical evidence is needed to evaluate which rtCGM parameter is the best predictor of the occurrence of severe hypoglycaemic events in the future (SH; defined as events that need third party assistance for recovery). Therefore, we analysed data of the control group of the HypoDE-study, a randomised controlled trial that has shown that rtCGM had a beneficial impact on the occurrence of low glucose events (LGE: <55 mg/dl) in patients with type 1 diabetes on multiple daily injections (MDI) and hypoglycaemia problems.

We analysed the ability of the rtCGM-parameters proposed by the consensus statement at baseline to predict the occurrence of SH in the HypoDE-study.

MATERIALS AND METHODS

Participants of the HypoDE-study all had hypoglycaemia problems either because they experienced a SH event in the past 12 months or because they had a hypoglycaemia unawareness. Participants in the control group were equipped with a masked rtCGM system (Dexcom G4) for 4 weeks in the baseline phase. In the consecutive 26 weeks of the therapy- and follow-up phase (T/F-phase), they continued with blood glucose measurements. Events of SH were assessed via Adverse Events forms and were validated by the treating physician.

The area under the Receiver Operating Characteristics (ROC) curves of different rtCGM parameters were used to compare the predictive performance of these parameters. Additionally, cut-off values were determined. The following parameters were used (based on the consensus statement):

- Percentage and number (per 28 days) of glucose values ≤ 69 mg/dl (but ≥ 54 mg/dl)
- Percentage and number (per 28 days) of glucose values ≤ 53 mg/dl
- Low blood glucose index (LBGI)
- Number (per 28 days) of events with glucose values ≤ 53 mg/dl for more than 120 consecutive minutes

Additionally, the following CGM-parameters were analysed:

- Percentage of glucose values ≤ 70 mg/dl, ≤ 55 mg/dl, ≤ 45 mg/dl, 71-180 mg/dl (in range)
- Coefficient of variation and standard deviation as markers of glucose variability
- Mean sensor glucose

RESULTS

The analysis was based on rtCGM data of 66 participants of the control group of the HypoDE-study (see Table 1). Exposure to hypoglycaemia and glucose variability are described in Table 2.

Occurrence of severe hypoglycaemia:

- During the T/F-phase, 39 episodes of SH were observed.
- At least one episode of SH occurred in 14 of the 66 participants (21.2%).

Screening performance of severe hypoglycaemic events (Figure 1, Table 3):

- Overall, area under the ROC curves for all six parameters of the consensus statement were significantly better in predicting events of SH than the prediction by chance.
- The additional CGM parameters achieved the following area under the ROC curves:
  - Percentage of glucose values ≤ 70 mg/dl: 0.69 (95% CI 0.54 – 0.85, p=0.027)
  - Percentage of glucose values ≤ 55 mg/dl: 0.68 (95% CI 0.52 – 0.85, p=0.034)
  - Percentage of glucose values ≤ 45 mg/dl: 0.66 (95% CI 0.49 – 0.84, p=0.060)
  - Percentage of glucose values in range: 0.59 (95% CI 0.44 – 0.75, p=0.293)
  - Coefficient of variation: 0.67 (95% CI 0.49 – 0.84, p=0.056)
  - Standard deviation: 0.51 (95% CI 0.36 – 0.67, p=0.863)
  - Mean sensor glucose: 0.70 (95% CI 0.55 – 0.86, p=0.022)

Cut-off values to detect a heightened risk for severe hypoglycaemia (Table 3):

- The cut-off value of percentage of glucose values ≤ 69 mg/dl indicate that values higher than 4.6% can be used to detect patients with an elevated risk for SH with a sensitivity of 71.4% and a specificity of 66.6%.
- One event of prolonged (>120 min) glucose values ≤ 53mg/dl is able to detect elevated risk for SH with a sensitivity of 79.0%, but only has a specificity of 56.0%.

Hazard ratio for the incidence of severe hypoglycaemic events (Figure 2):

- With every unit increase in the LBGI, the risk for an SH event is increased by 67% (Hazard ratio [HR] = 1.67; 95% CI 1.11 to 2.53).
- The risk for an SH event is increased by 25% (HR = 1.25; 95% CI 1.01 to 1.53) with every percentage point ≤ 69 mg/dl, whereas with every additional glucose event ≤ 69 mg/dl, the risk for an SH event is only increased by 4% (HR = 1.04; 95% CI 1.01 to 1.07)

CONCLUSION

All parameters that were derived from the consensus statement can be used to predict the future risk of a severe hypoglycaemic event. They had a similar area under the ROC-curve and overlapping confidence intervals. Thus, there is no clear advantage of a specific parameter out of these 6 parameters recommended by the consensus statement in this specific HypoDE sample.

In contrast, percentage of glucose values ≤ 45 mg/dl and between 71 – 180 mg/dl as well as markers of glycaemic variability were not significant in predicting future risk for SH.

The proposed cut-off values for the CGM-parameters can be used in clinical practice to identify people with diabetes with an increased risk for SH events.

However, it must be kept in mind that the suggested cut-off values and hazard ratios are derived from a post-hoc analysis of the HypoDE study, which included only people with hypoglycaemia problems. Therefore, the generalisability is clearly limited. There is a need for prospective studies with different study populations to corroborate the suggested cut-off values.

In summary, a systematic analysis of CGM while in use can guide clinicians and patients to timely identify an elevated risk for SH, before such an event occurs.

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1 Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017; 40(12): 1631-40.

Table 1: Sample characteristics

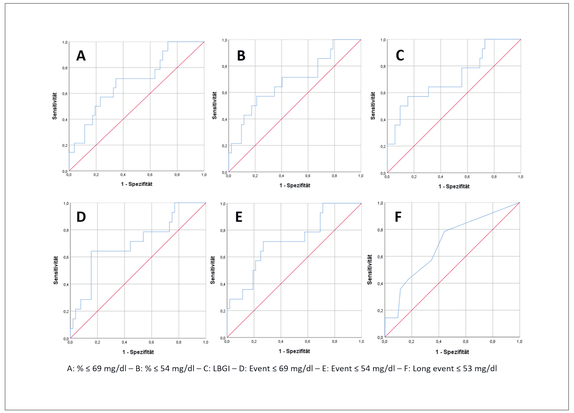
M ± SD, n (%)	Control group of the HypoDE-study (n = 66)
Age, years	47.3 ± 10.1
Gender Male Female	 45 (68.2%) 21 (31.8%)
Body-mass index, kg/m²	26.0 ± 4.7
Diabetes duration, years	20.8 ± 13.1
HbA1c, %	7.4 ± 1.0
Long-term complications At least one Mean number	 9 (13.6%) 0.2 ± 0.7
Severe hypoglycaemia in the past 12 months	40 (60.6%)
Hypoglycaemia unawareness	60 (90.1%)

Table 2: Glycaemic characteristics at baseline

M ± SD	Control group of the HypoDE-study (n = 66)
CGM-parameters derived from the consensus statement	
% ≤ 69 mg/dl	4.7 ± 2.9
% ≤ 53 mg/dl	3.1 ± 3.1
LBGI	1.9 ±1.4
Number of glucose events ≤ 69 mg/dl per 28 days	23.8 ± 12.9
Number of glucose events ≤53 mg/dl per 28 days	12.0 ± 10.1
Number of long glucose events ≤53 mg/dl per 28 days	1.6 ± 2.4
Additional CGM-parameters	
Percentage of glucose values in various ranges ≤ 70 mg/dl ≤ 55 mg/dl ≤ 40 mg/dl 71 – 180 mg/dl	 8.1 ± 5.9 3.6 ±3.4 1.0 ± 1.5 59.1 ± 13.3
Glucose variability CV SD	 40.5 ± 7.0 63.3 ± 13.8
Sensor glucose	157.0 ± 26.5

Table 3: Area under the ROC-curves, cut-off values and screening performance of the various CGM-parameters (derived from the consensus statement)

CGM Parameter	Area under ROC (95% CI)	Cut-off value	Sensitivity	Specificity
% ≤ 69 mg/dl	0.69 (0.54 – 0.83)	4.6%	71.4%	66.6%
% ≤ 53 mg/dl	0.69 (0.52 – 0.85)	2.4%	71.4%	59.6%
LBGI	0,70 (0.55 -0.86)	1.6	71.4%	57.7%
Number of glucose events ≤ 69 mg/dl per 28 days	0.72 (0.54 – 0.87)	28	71,4%	69,6
Number of glucose events ≤53 mg/dl per 28 days	0.73 (0.55 – 0.86)	10.5	71.4%	59.6%
Number of long glucose events ≤53 mg/dl per 28 days	0.69 (0.53 – 0.85)	1	79.0%	56.0%



A: % ≤ 69 mg/dl – B: % ≤ 54 mg/dl – C: LBGI – D: Event ≤ 69 mg/dl – E: Event ≤ 54 mg/dl – F: Long event ≤ 53 mg/dl

Figure 1: Screening characteristics of the various CGM-parameters (derived from the consensus statement)

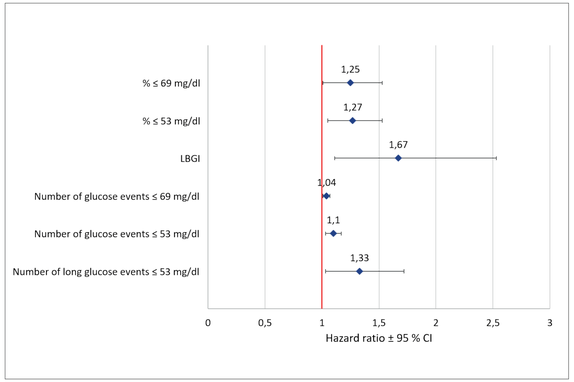


Figure 2: Hazard ratios for the incidence of severe hypoglycaemic events

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