Identifying People at Risk for Severe Hypoglycemia by CGM in a Sample of People with Reduced Hypoglycemia Awareness

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ABSTRACT

It is well known that people with type 1 diabetes (pw1d) and hypoglycemia unawareness have an increased risk for severe hypoglycemia (SH); however, it is unknown if continuous glucose monitoring (CGM) helps to prospectively evaluate the risk of SH in such patients. We analyzed CGM recordings of 126 participants on MDI in the HypoDE study with hypoglycemia unawareness wearing blinded CGM (DexCom Gen 4) for 28 days (age 46.5±11.5 yrs., 36.5% female, HbA1c 7.5±1.0%, unawareness score 5.0±1.1). From these subjects, 65 (51.6%) reported occurrence of SH in the last year prior to study start.

Duration (min per day)	≤70 mg/dl	≤60 mg/dl	≤55 mg/dl	≤50 mg/dl	# of glucose events ≤55 mg/dl per 28 days
Without SH (median – IQR)	69.0 (27.0-114.5)	34.3 (13.1-70.2)	21.6 (8.1-48.9)	12.7 (3.7-27.9)	6.3 (2.1-13.1)
With SH (median – IQR)	102.6 (55.5-197.4)	53.1 (24.9-125.3)	38.3 (15.7-92.3)	26.2 (9.8-65.9)	11.5 (4.6-25.3)
P	0.003	0.001	0.001	0.001	0.001
Area under ROC-curve	0.67 (0.58-0.76)	0.67 (0.57-0.76)	0.66 (0.57-0.76)	0.67 (0.57-0.76)	0.65 (0.56-0.75)
Cut-off value	93.0 min	43.6 min	30.2 min	19.2 min	9.4 events
Sensitivity/Specificity	53.0%/61.7%	57.8%/57.4%	59.4%/62,3%	62.5%/62.3%	60.9%/60.7%

IQR = inter quartile range

In a high-risk group of pw1d and hypoglycemia unawareness, CGM data on the exposure regarding hypoglycemic glucose values or number of hypoglycemic events ≤55 mg/dl predict the occurrence of SH. ROC analyses suggested meaningful cut-off values for the duration of hypoglycemic episodes, respectively the number of hypoglycemic events. These cut-off values can facilitate the identification of people with an elevated risk for SH even in a hypoglycemic high-risk group with reasonable sensitivity and specificity.

BACKGROUND

It is well known that people with type 1 diabetes and hypoglycemia unawareness have an increased risk for severe hypoglycemia (SH), defined as the need of third party assistance for recovery. However, it is unknown to which extent continuous glucose monitoring (CGM) can provide data to identify people who experienced an episode of severe hypoglycemia in the past year in this high-risk group. Therefore, we analyzed baseline data of the HypoDE study to examine the following problems:

1. Are the hypoglycemic CGM profiles different in people with and without severe hypoglycemia?
2. Can CGM Data be used to identify people with severe hypoglycemia in this high-risk group?
3. What is the screening performance of the hypoglycemic CGM profile to identify people with severe hypoglycemia?

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. Each participant used a blinded CGM system (Dexcom G4) for 28 days. We used the duration of time per day spent in different hypoglycemic levels (≤ 70 mg/dl, ≤ 60 mg/dl, ≤ 55 mg/dl, ≤ 50 mg/dl) and the number of hypoglycemic events with glucose readings of ≤ 55 mg/dl for at least 20 minutes as hypoglycemic CGM profiles. We used Receiver Operating Characteristics curves (ROC) to evaluate the ability of the above mentioned parameters to identify people with SH. We calculated sensitivity, specificity as well as positive and negative predictive values to determine the screening performance of these parameters.

RESULTS

- In table 1 the sample characteristics are described. Participants had a rather long diabetes duration and a rather good glycemic control as indicated by a mean A1c of 7.5%. People with SH had a longer diabetes duration, a lower A1c, a higher hypoglycemia unawareness score, more hypoglycemia related worries and avoidance behavior as well as higher diabetes-related distress.
- Table 2 and figure 1 provide the hypoglycemic CGM profile in people with and without SH. Using parametric and non-parametric statistics indicated that all parameters of the hypoglycemic CGM profile were significantly different for people with and without SH.
- The ROC and the area under the ROC are depicted in figures 2 and 3. The ROC was clearly above the 0.5 diagonal line (figure 2), indicating better screening performance than a classification by chance. The 95% confidence interval of the area under the ROC does not cut the 0.5 line (figure 3), which indicates that the mentioned parameters of the hypoglycemic profile can significantly better identify people with SH than a classification by chance.
- Sensitivity and specificity as well as positive and negative predictive values are shown in figures 4 and 5. Although sensitivity and specificity are reasonable high, there is still room for improvement.
- In figure 6, the hazard ratio of SH is shown. The risk of SH is roughly doubled if one of the parameters show an increase of one standard deviation.

CONCLUSION

In a high-risk group of patients with type 1 diabetes and hypoglycemia unawareness, hypoglycemic CGM profiles can clearly discriminate people with and without severe hypoglycemia. The screening performance of this hypoglycemic CGM profile is significantly better than a classification by chance. There is also a high concordance of different parameters of the hypoglycemic profile. The choice of the hypoglycemic cut-off-values does not play a decisive role, since the screening performance of all indicators of the hypoglycemic profile are rather similar. However, the sensitivity and especially the specificity showed room for improvement. Since the screening performance was tested in a high-risk group of people with type 1 diabetes it cannot be ruled out that the sensitivity, specificity as well as the positive and negative predictive values would have been different in a sample of people with good hypoglycemia awareness. The hazard ratios showed a two-fold increase of the risk of severe hypoglycemia when the parameters of the hypoglycemic CGM profiles increased by one standard deviation. Such analyses might help to translate results of CGM in more meaningful information for the patient.

Table 1: Sample characteristics

Sample characteristics Mean (±SD) or %	All N=126	Without SH N=61	With SH N=65	p
Age in yrs.	46.5 (±11.6)	46.1 (± 12.4)	46.9 (± 10.8)	.680
% female	36.5 %	34.4%	38.5%	.641
Diabetes duration in yrs.	20.5 (±13.7)	17.9 (±13.1)	22.8 (±14.0)	.046
A1c in %	7.5 (± 1.0)	7.7 (±0.9)	7.3 (±1.0)	.035
Hypglycemia Unawareness Score	5.0 (±1.1)	4.7 (±0.7)	5.2 (±1.3)	.013
Insulin dose in IU/KG	0.58 (±0.25)	0.55 (±0.19)	0.61 (±0.31)	.191
HFS II - worry scale	32.3 (±15.5)	29.0 (±15.8)	35.4 (±14.6)	.021
HFS II - behavior scale	20.8 (±9.0)	18.9 (±8.4)	22.5 (±9.3)	.025
Diabetes Distress Scale	2.5 (±0.8)	2.3 (±0.8)	2.7 (±0.8)	.005

Table 2: Hypoglycemic CGM profiles

Sample Charactristics Mean (±SD)	All N=126	Without SH N=61	With SH N=65	p
CGM wearing time (± SD) in days	26.8 (±4.3)	26.5 (±2.6)	27.4 (±4.8)	0.159
Duration of glucose ≤ 70 mg/dl (± SD) per day in minutes	109.0 (±91.4)	78.7 (±61.7)	136.2 (±105.4)	<.001
Duration of glucose ≤ 60 mg/dl (± SD) per day in minutes	65.2 (±65.5)	44.1 (±40.8)	84.9 (±77.9)	<.001
Duration of glucose ≤ 55mg/dl (± SD) per day in minutes	47.9 (±53.4)	31.2 (±32.0)	63.6 (±64.4)	.001
Duration of glucose ≤ 50 mg/dl (± SD) per day in minutes	34.4 (±42.6)	20.8 (±24.1)	46.6 (±52.1)	.001
Number of events ≤ 55mg/dl (± SD) per 28 days	12.7 (±11.8)	9.1 (±8.4)	16.0 (±13.4)	.001

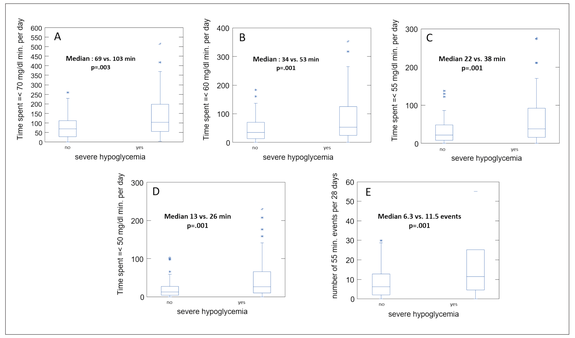

Figure 1: Difference of duration of different hypoglycemic phases (A-D) for number of ≤ 55 mg/dl hypoglycemic events (E) in people with and without severe hypoglycemia

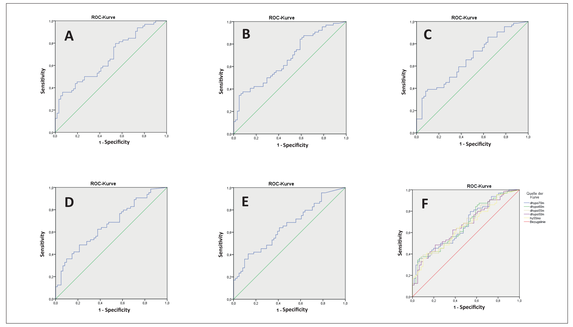

Figure 2: ROC curves of the screening performance of the duration of different hypoglycemic profiles for the identification of participants with every hypoglycemia (A ≤ 70 mg/dl; B ≤ 60 mg/dl; C ≤ 55 mg/dl; D ≤ 50 mg/dl; E # of ≤ 55 events; F = all ROC)

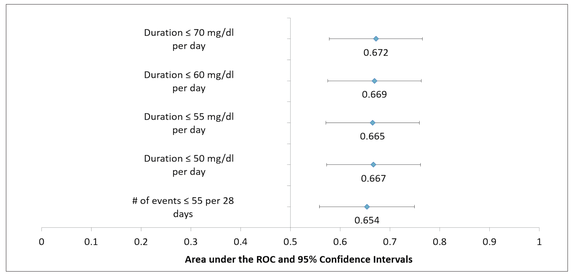

Figure 3: Area under the receiver operating curves for duration of different hypoglycemic ranges or for number of events ≤ 55 mg/dl with 95% confidence intervall

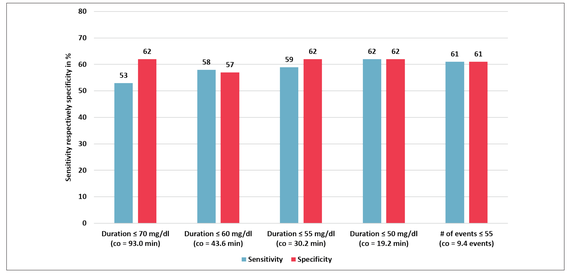

Figure 4: Sensitivity and specificity of CGM data for identification of people with severe hypoglycemia

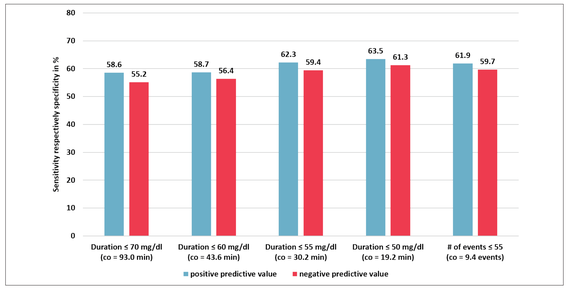

Figure 5: Positive and negative predictive values of CGM data for identification of people with severe hypoglycemia

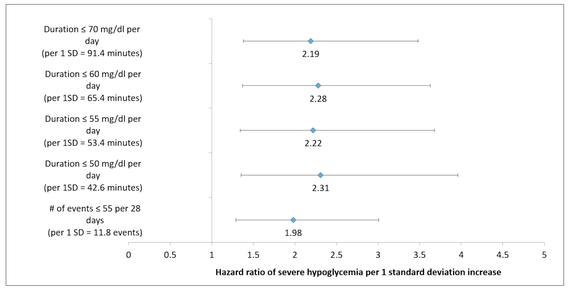

Figure 6: Hazard ratio of SH in dependence from an increase of different parameters of the CGM profile by 1 SD

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