DOI: 10.1111/dme.14362

Research: Complications

People with type 1 diabetes and impaired awareness of hypoglycaemia have a delayed reaction to performing a glucose scan during hypoglycaemia: a prospective observational study

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Accepted 1 July 2020

Abstract

Aims Considering that people with type 1 diabetes and impaired awareness of hypoglycaemia (IAH) have a delayed perception of hypoglycaemia, the question arises whether they perform scans later in case of hypoglycaemia than people without IAH. We assessed whether time to performing a scan after reaching hypoglycaemia while using a flash glucose monitoring (flash GM) system is different in people with IAH compared with people without IAH.

Methods Ninety-two people with type 1 diabetes [mean (± SD) age 42 ± 14 years, HbA_{1c} 57 ± 9 mmol/mol] using a flash GM system for 3 months were included. Flash GM data were assessed for time until scan after reaching hypoglycaemia level 1 (< 3.9 mmol/l) and level 2 (< 3.0 mmol/l) and compared for type 1 diabetes with vs. without IAH via unpaired *t*-test/Mann–Whitney *U* test ($P < 0.05$).

Results Significant differences were found only for the delay between reaching hypoglycaemia and scan between people with and without IAH for Gold score [hypoglycaemia level 1: IAH 78 (51–105) min vs. without IAH 63 (42–89) min, $P = 0.03$; night-time hypoglycaemia level 2: IAH 140 (107–227) min vs. without IAH 96 (41–155) min, $P = 0.004$] and Pedersen-Bjergaard score [hypoglycaemia level 1: IAH 76 (52–97) min vs. without IAH 54 (38–71) min, $P = 0.011$; night-time hypoglycaemia level 1: IAH 132 (79–209) min vs. without IAH 89 (59–143) min, $P = 0.011$; night-time hypoglycaemia level 2: IAH 134 (66–212) min vs. without IAH 80 (37–131) min, $P = 0.002$). Data are shown as median (i.q.r.).

Conclusions Time until scan after reaching hypoglycaemia might be an objective assessment tool for IAH, but needs to be investigated comprehensively in future studies.

Diabet. Med. 37, 2153–2159 (2020)

Introduction

Impaired awareness of hypoglycaemia (IAH), defined as the diminished ability to perceive the onset of acute hypoglycaemia, affects 20–25% of people with type 1 diabetes and increases the risk of severe hypoglycaemia requiring third-party assistance sixfold [1]. The frequency of recurrent hypoglycaemia impairs counter-regulatory hormone responses to hypoglycaemia and represents a major cause of attenuated hypoglycaemia symptoms [1]. Unfortunately, long-standing diabetes *per se* was found to be linked to an increased risk of developing IAH [2]. In clinical studies and real-life conditions, assessment of IAH is based mainly on scoring systems such as the Gold score, Clarke score and Pedersen-Bjergaard score [3–5]. These scoring systems have been shown to assess IAH in people with type 1 diabetes, however, objective measurements to evaluate IAH for clinical settings are not currently available. Importantly, early diagnosis of IAH may immediately reduce the risk of severe hypoglycaemia because individuals with type 1 diabetes often do not recognize that they already have developed IAH.

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What's new?

- Assessment of impaired awareness of hypoglycaemia (IAH) is based mainly on scoring systems such as the Gold score, Clarke score and Pedersen-Bjergaard score.
- Our data revealed that time until scan after reaching hypoglycaemia while using a flash glucose monitoring system (flash GM) is delayed significantly in people with type 1 diabetes and IAH compared with those with type 1 diabetes without IAH, when IAH was assessed by Gold score and Pedersen-Bjergaard score.
- From a clinical point of view, our method might serve as a tool for the early and objective identification of IAH in people with type 1 diabetes.

To improve glycaemic control by means of increasing the time in range (3.9–10 mmol/l) and decreasing the times above and below range, several interstitial glucose-monitoring systems have been recommended for people with type 1 diabetes [6]. In contrast to real-time glucose monitoring, flash glucose monitoring (flash GM) requires actively determining glucose level via a scan. Concomitant with the glucose value, a trend arrow is displayed on the reader [7]. In addition, a retrospective glucose curve is displayed showing historical glucose levels for past hours.

Currently, only one flash GM system is available on the market. This system does not require calibration as it is factory calibrated and users rely on sensor values when treatment decisions are made. The efficacy of flash GM systems was proven by reduction in HbA_{1c} levels, frequency and duration of hypoglycaemia and improved quality of life [8,9]. Use of flash GM significantly reduced time spent in hypoglycaemia without deteriorating HbA_{1c} in people with type 1 diabetes [10]; real-time glucose monitoring had significantly greater benefits in reducing hypoglycaemia than flash GM in those with IAH [11]. This advantage of real-time glucose monitoring over flash GM is mainly induced by hypoglycaemia threshold alerts that are generated automatically when a defined value is reached. Because there are no automatic alerts to warn of impending hypoglycaemia, people with type 1 diabetes still need to perform regular glucose scans when using flash GM. Considering that people with type 1 diabetes and IAH have a delayed or missing perception of hypoglycaemia, it can be assumed that performance of scans is delayed in comparison with individuals with normal hypoglycaemia awareness. However, the nonexistent hypoglycaemia alert highlights potential new features of flash GM: time until a glucose scan is performed while being within the hypoglycaemic range might be used as an objective screening tool for hypoglycaemia unawareness.

The aim of this prospective secondary outcome analysis was to investigate whether people with type 1 diabetes and IAH show a different 'scan behaviour' when reaching hypoglycaemia compared with people with type 1 diabetes and normal hypoglycaemia awareness.

Participants and methods

This prospective, observational, predefined secondary outcome analysis was performed in line with the Declaration of Helsinki and Good Clinical Practice. The study was approved by the ethics committee of the Medical University of Graz (29-522 ex 16/17) and local health authority (and registered at the German Clinical Trials Register: DRKS.de; DRKS00013667). The primary outcome of the larger trial and its accompanied sample size estimation were based on the accuracy of estimated HbA_{1c} value as given by flash GM vs. measured HbA_{1c}.

Study procedures

People with type 1 diabetes using a flash GM system for at least 3 months with over 80% of sensor data available were included. Regular diabetes self-management with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) was performed over the 3-month period. Historical interstitial glucose data were downloaded from the flash GM system for the entire 3-month period. Because of default specifications, glucose data were available as 15-min average values and were linearly interpolated to a 1-min interval to allow analysis at the required high resolution. Hypoglycaemia was defined in line with current guidelines: level 1 (< 3.9 mmol/l) and level 2 (< 3.0 mmol/l). Time until a scan was performed after reaching hypoglycaemia was assessed in the overall data set and stratified for daytime (06.00 a.m. to 11.59 p.m.) and night-time (12.00 a.m. to 05.59 p.m.). If hypoglycaemia occurred without performing a subsequent scan then these values were excluded from the calculations for time to scan. If the duration of a hypoglycaemic episode was ≥ 8 h without performing a scan then these values were excluded, presuming a false-positive hypoglycaemia reading.

Standard routine assessment for IAH was performed using three validated questionnaires (Gold score [3], Clarke score [4] and Pedersen-Bjergaard score [12,13]) after the 3-month flash GM use. The Gold score included the question 'Do you know when your hypos are commencing?' Results are expressed by a 7-point Likert scale, where 1 = 'always aware' and 7 = 'never aware' (≥ 4 = IAH). The Clarke score consists of eight questions defining participant's exposure to moderate and severe hypoglycaemia. It also assesses the threshold for and symptomatic responses to hypoglycaemia (≥ 4 = IAH). The Pedersen-Bjergaard score poses the question 'Can you feel when you are low?' requiring the selection of one response from 'always', 'usually', 'sometimes' or 'never'. People who answer 'always' are considered to be hypoglycaemia aware; all others are classified as having IAH. Additionally, based on the assessment of IAH for each

questionnaire, people with IAH vs. people without IAH were compared for number of scans per day, number, duration and mean glucose concentration during hypoglycaemia levels 1 (< 3.9 mmol/l) and 2 (< 3.0 mmol/l) [14].

Statistical analyses

Data were assessed for distribution by Shapiro-Wilk testing. Group differences (IAH vs. without IAH) were investigated by means of unpaired *t*-test or Mann–Whitney *U* test. Comparison of glycaemic ranges [time below range (TBR) 2, < 3.0 mmol/l; TBR 1, 3.0– < 3.9 mmol/l; time in range (TIR), 3.9–10.0 mmol/l; time above range (TAR) 1, >10.0–13.9 mmol/l; TAR 2, >13.9 mmol/l] for the three different IAH assessment scores with respect to IAH vs. without IAH was analysed by two-way analysis of variance (ANOVA) with Sidak's multiple comparison test.

Data were analysed by using statistical software packages Prism v. 8.0 (GraphPad, La Jolla, CA, USA) and SPSS Statistics v. 25 (IBM, Armonk, NY, USA) ($P < 0.05$). Data are shown as mean ± SD or median (i.q.r.) unless specified otherwise. A receiver operating characteristics (ROC) analysis was performed via Wilson/Brown method assessing the sensitivity and specificity for the time until performing a scan after reaching hypoglycaemia level 2 (< 3.0 mmol/l) during the night-time as assessed by means of Gold score.

Results

Of 100 people with type 1 diabetes who were assessed for eligibility, eight did not want to complete hypoglycaemia questionnaires for personal reasons. Therefore, 92 participants (46 women and 46 men) were included. Participant characteristics were as follows: age 42 ± 14 years, BMI 25.1 ± 4.0 kg/m^2, HbA_{1c} 57 ± 9 mmol/mol (7.3 ± 0.8%) and duration of type 1 diabetes of 19 ± 13 years. Some 73 participants were using MDI and 19 CSII as standard therapy with a total daily insulin dose of 43 ± 17 IU with (all using insulin analogues). Participants were already familiar with flash GM as their pre-study flash GM use was 309 ± 223 days. During the entire study period, no severe hypoglycaemia event requiring external assistance occurred.

Assessment of IAH

Assessment of IAH resulted in 18 of 92 participants (20%) having IAH as judged by the Gold score, 12 participants (13%) as judged by the Clarke score and 47 participants (50%) as judged by the Pedersen-Bjergaard score. Pedersen-Bjergaard score showed a significantly higher number of people with IAH compared with both the Gold score ($P < 0.001$) and Clarke score ($P < 0.001$) (Table S1). A similar number of people with IAH was found when using the Gold score and the Clarke score ($P = 0.944$). When IAH was assessed by means of Gold score, no significant differences were found for age [IAH: 37 (25–51) years vs. without IAH: 45 (30–56) years; $P = 0.316$] and duration of diabetes [IAH: 22 (13–28) years vs. without IAH: 16 (9–29) years; $P = 0.198$]. No significant differences were found for the Clarke score when comparing age [IAH: 35 (26–50) years vs. without IAH: 44 (28–55) years; $P = 0.372$] and duration of diabetes [IAH: 23 (13–28) years vs. without IAH: 16 (10–29) years; $P = 0.369$]. Similar results were found for the Pedersen-Bjergaard score with no significant differences for age [IAH: 45 (31–53) years vs. without IAH: 39 (27–56) years; $P = 0.601$] and duration of diabetes [IAH: 21 (10–32) years vs. without IAH: 15 (9–25) years; $P = 0.149$]. Eight people with IAH were assessed as having IAH in all three scoring tools, 11 people with IAH in two scoring tools (agreement Gold score/Clarke score in two, Gold score/Pederson-Bjergaard score in seven and Clarke score/Pederson-Bjergaard score in two) and 30 people with IAH in only one scoring tool (one person via Gold score and 29 via Pederson-Bjergaard score). ROC analysis for the time until performing a scan after reaching hypoglycaemia level 2 (< 3.0 mmol/l) resulted in an area under the ROC curve of 0.79 ($P < 0.001$) with a sensitivity and specificity of each 73% (likelihood ratio 2.7) at > 135 min.

Time until performing a scan and IAH

When comparing people with and without IAH based via Gold score, significant differences were found for the time until performing a scan after reaching hypoglycaemia level 1 [IAH: 78 (51–105) min vs. without IAH: 63 (42–89) min; $P = 0.029$] in the overall data set and during the night-time for hypoglycaemia level 2 (IAH: 140 (107–227) min vs. without IAH: 96 (41–155) min; $P = 0.004$] (Table 1). No significant differences were found in the comparison of IAH and without IAH when assessing IAH by means of Clarke score (Table 2). When comparing IAH and without IAH based on the Pederson-Bjergaard score, significant differences were found for the time until performing a scan after reaching hypoglycaemia level 1 [IAH: 76 (52–97) min vs. without IAH: 54 (38–71) min; P = 0.011] and when stratified for night-time hypoglycaemia level 1 [IAH: 132 (79–206) min vs. without IAH: 89 (59–143) min; $P = 0.011$] and night-time hypoglycaemia level 2 [IAH: 134 (66–212) min vs. without IAH: 80 (37–131) min; $P = 0.002$) (Table 3).

Scans per day in comparison of IAH vs. without IAH

Independent of the type of IAH assessment method, participants with IAH performed a similar number of scans per day compared with those with IAH (IAH: 9.8 scans/day vs. without IAH: 11.7 scans/day; $P = 0.095$). Differences between scans per day in regard to the type of IAH assessment score were found for the Gold score during the night-time period and for the Pedersen-Bjergaard score for overall values and daytime period (Fig. 1).

Table 1 Comparison of IAH vs. without IAH based on the Gold score method for time until performing a scan after reaching hypoglycaemia level 1 and level 2, stratified for daytime and night-time

	Gold score IAH (n = 18)	Gold score without IAH (n = 74)	P-value
Hypoglycaemia level 1 (< 3.9 mmol/l)	78 (51–105)	63 (42–89)	0.029
Hypoglycaemia level 2 (< 3.0 mmol/l)	103 (55–119)	96 (41–155)	0.059
Daytime hypoglycaemia level 1 (< 3.9 mmol/l)	66 (36–74)	42 (27–61)	0.084
Daytime hypoglycaemia level 2 (< 3.0 mmol/l)	59 (32–83)	42 (27–69)	0.178
Night-time hypoglycaemia level 1 (< 3.9 mmol/l)	127 (84–191)	104 (61–175)	0.169
Night-time hypoglycaemia level 2 (< 3.0 mmol/l)	140 (107–227)	96 (41–155)	0.004

Values are given as median (IQR) time (min) until scan after reaching hypoglycaemia.
IAH, impaired awareness of hypoglycaemia.

Table 2 Comparison of IAH vs. without IAH based on the Clarke score method for time until performing a scan after reaching hypoglycaemia level 1 and level 2, stratified for daytime and night-time

	Clarke score IAH (n = 12)	Clarke score without IAH (n = 80)	P-value
Hypoglycaemia level 1 (< 3.9 mmol/l)	80 (51–100)	59 (43–87)	0.150
Hypoglycaemia level 2 (< 3.0 mmol/l)	76 (52–107)	66 (43–103)	0.496
Daytime hypoglycaemia level 1 (< 3.9 mmol/l)	63 (37–70)	44 (28–63)	0.150
Daytime hypoglycaemia level 2 (< 3.0 mmol/l)	58 (33–66)	44 (27–70)	0.509
Night-time hypoglycaemia level 1 (< 3.9 mmol/l)	116 (74–203)	106 (63–171)	0.628
Night-time hypoglycaemia level 2 (< 3.0 mmol/l)	121 (98–170)	106 (42–172)	0.266

Values are given as median (IQR) time (min) until scan after reaching hypoglycaemia.
IAH, impaired awareness of hypoglycaemia.

Table 3 Comparison of IAH vs. without IAH based on the Pedersen-Bjergaard score for time until performing a scan after reaching hypoglycaemia level 1 and level 2, stratified for daytime and night-time

	Pedersen-Bjergaard score IAH (n = 47)	Pedersen-Bjergaard score without IAH (n = 45)	P-value
Hypoglycaemia level 1 (< 3.9 mmol/l)	76 (52–97)	54 (38–71)	0.011
Hypoglycaemia level 2 (< 3.0 mmol/l)	75 (49–111)	55 (41–89)	0.093
Daytime hypoglycaemia level 1 (< 3.9 mmol/l)	56 (34–68)	38 (24–53)	0.124
Daytime hypoglycaemia level 2 (< 3.0 mmol/l)	53 (32–70)	38 (26–64)	0.151
Night-time hypoglycaemia level 1 (< 3.9 mmol/l)	132 (79–206)	89 (59–143)	0.011
Night-time hypoglycaemia level 2 (< 3.0 mmol/l)	134 (66–212)	80 (37–131)	0.002

Values are given as median (IQR) time (min) until scan after reaching hypoglycaemia.
IAH, impaired awareness of hypoglycaemia.

Characteristics of hypoglycaemia in comparison of IAH vs. without IAH

When comparing hypoglycaemia characteristics for number of hypoglycaemic episodes and glucose level during hypoglycaemia between IAH and without IAH assessed by Gold score, statistically, albeit not clinically, significant differences were found only for median glucose concentration during hypoglycaemia level 1 [IAH: 3.4 (3.3–3.5) mmol/l vs. without IAH: 3.5 (3.3–3.6) mmol/l; P = 0.031]. No significant differences between groups were found for the number of episodes of hypoglycaemia at level 1 (P = 0.468) and at level 2 (P = 0.138) as well as median glucose concentration at level 2 (P = 0.052). When defining IAH based on the Clarke score, hypoglycaemia level 1 was accompanied by a lower glucose concentration in IAH [IAH: 3.3 (3.2–3.4) mmol/l, without IAH: 3.5 (3.3–3.6) mmol/l; P = 0.010]. Additionally, those with IAH had a higher daily number of hypoglycaemic episodes at level 2 [IAH: 0.61 (0.33–0.67) vs. without IAH: 0.26 (0.13–0.50); P = 0.044]. No significant differences were found for the median glucose concentration during hypoglycaemia level 2 (P = 0.111) and number of events at level 1 (P = 0.145). Based on the Pedersen-Bjergaard score, no significant differences were found for the number of hypoglycaemic episodes level 1 (P = 0.399) and level 2 (P = 0.890) and median glucose concentration during hypoglycaemia level 1 (P = 0.167) and for level 2 (P = 0.505).

TBR 2 for people with IAH was significantly higher when assessed by Gold score compared with Pedersen-Bjergaard score (P = 0.002), while no significant differences were found for comparison of any other assessment score for TBR 2 nor TBR 1 (P > 0.05). No significant differences were found for any assessment score for TBR 2 and TBR 1 in people without IAH (P > 0.05). No significant differences were found for the type of assessment score for TIR

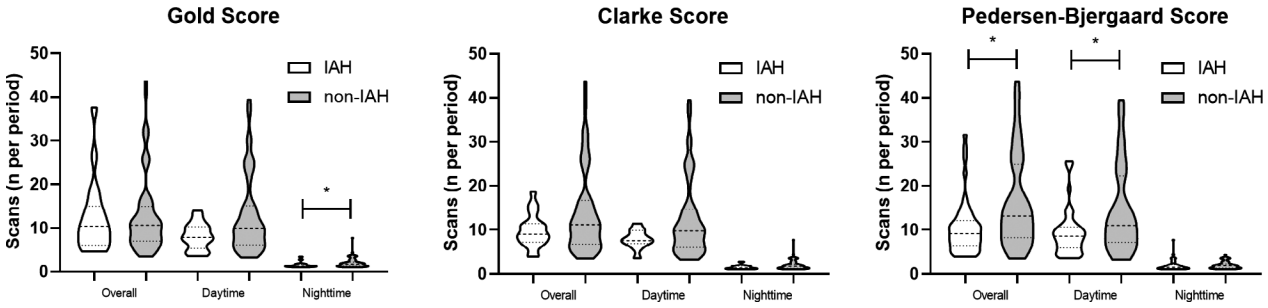

FIGURE 1 Comparison of scans per day, daytime and night-time performed in people with type 1 diabetes without impaired hypoglycaemia awareness () vs. those with impaired awareness of hypoglycaemia (IAH) assessed by means of the Gold score (a), Clarke score (b) and Pedersen-Bjergaard score (c).

(P = 0.883), TAR 1 (P = 0.985) and TAR 2 (P = 0.984) for people with IAH and without IAH (Fig. S1).

Cases in which hypoglycaemia lasted > 8 h (data exclusion) were similar for IAH and without IAH when assessed via Gold score (IAH: 0.4 ± 0.9 vs. without IAH: 0.4 ± 0.8; P = 0.537), Clarke score (IAH: 0.6 ± 1.0 vs. without IAH: 0.4 ± 0.8; P = 0.331) and Pedersen-Bjergaard score (IAH: 0.3 ± 0.8 vs. without IAH: 0.5 ± 0.9; P = 0.305).

Discussion

This is the first analysis showing that people with type 1 diabetes and IAH have a delayed response to perform a glucose scan during hypoglycaemia when using a flash GM. In our study, people with IAH were older and had a longer diabetes duration when compared against people without IAH that might reflect the pathophysiological 'non-response' to hypoglycaemia, as expected for long duration type 1 diabetes [1].

Similar to our findings, Streja [15] found that maximal duration of hypoglycaemia was the strongest predictor for IAH when assessed by means of CGM system. In that study it was found that detection of hypoglycaemia with a duration of > 90 min identified people who had IAH with 88% specificity and 75% sensitivity. From our point of view, assessing IAH during the daytime might be biased by fortuitous hypoglycaemia detection. Hence in our study, ROC analysis was performed for the time until performing a scan during hypoglycaemia level 2 (< 3.0 mmol/l) for the nocturnal period, showing a sensitivity and specificity for each of 73% at > 135 min. Even though that the next generation of flash GM incorporating real-time low and high sensor glucose alerts is already available in some countries in Europe, the first generation of flash GM might still be used for the assessment of IAH.

Unfortunately, the three scoring systems applied in our study are indirect participant-reported assessments of IAH, which, although clinically validated, cannot in isolation qualify our method as an assessment tool for IAH. When IAH was assessed by Gold score and Pedersen-Bjergaard score, people with IAH showed significantly delayed scan behaviour to hypoglycaemia when compared with people without IAH. When IAH was classified based on the Clarke score, there was a tendency that people with IAH perform scans later during hypoglycaemia.

In line with previous studies [13,16], the Gold score and Clarke score showed similar percentages for the detection of IAH, whereas the Pedersen-Bjergaard score showed more people with IAH. As concluded by Geddes *et al.* [13] who observed that people with IAH had a longer duration of diabetes, had experienced more episodes of severe hypoglycaemia and recorded frequent mild hypoglycaemia, the Gold score and Clarke score might assess IAH more accurately.

Our study is not without limitations: fear of hypoglycaemia, which could have given further insight into our findings, potentially influencing behaviour regarding glucose scanning, was not assessed [17]. Additionally, flash GM systems show weaknesses in their performance during hypoglycaemia and high rates of change in glucose [18]. In general, flash GM shows a propensity to give lower sensor glucose readings than the actual blood glucose concentration [19], and the technological and physiological lag time for the glucose to diffuse from the blood into the interstitial space might have affected our results [20]. Taking into account that participants did not perform confirmatory blood glucose measurements, the false-positive and true-negative number of hypoglycaemic episodes cannot be investigated in our study. Furthermore, the question arises whether routine scanning behaviour at individual time points may have incidentally detected hypoglycaemic episodes. Taking the linear interpolation method into account as performed in our study, the duration of a gap (15 min) might be sufficient to experience a significant rate of change in the glucose beginning to return to the last sensor glucose level recorded, before any hypoglycaemia is detected [21]. Nevertheless, our findings are promising and further assessment might involve a prospective study in larger group of people with IAH.

Intriguingly, participants with and without IAH assessed by means of Gold score and Clarke score performed a similar number of scans per day. When assessment of IAH was based

on the Pedersen-Bjergaard score, those without IAH performed significantly more scans per day than those with IAH. Because the median difference in number of scans per day was four for the Pedersen-Bjergaard score, we expect that this habit might have influenced our results. In previous studies it was shown that a greater number of scans per day was linked to improved glycaemic control [22], we assume that the time to performing a scan after reaching hypoglycaemia might also be influenced by the number of scans per day. To mitigate the risk of including phases with false hypoglycaemia, phases with prolonged hypoglycaemia (> 8 h) without intercurrent scan were excluded from the analysis. Because the occurrence of these cases was similar between IAH and no IAH we can assume that this method has not influenced our findings. As shown in previous studies [13,23,24], people with type 1 diabetes and IAH are more prone to hypoglycaemia, which is also reflected by our data: participants with IAH spent longer time in hypoglycaemia accompanied by lower glucose levels depending on the scoring method.

Our study showed that people with type 1 diabetes and IAH spent longer in hypoglycaemia before performing a scan when using a flash GM. Furthermore, time to performing a scan after reaching hypoglycaemia level 2 (< 3.0 mmol/l) during the nocturnal period might be the strongest predictor for the assessment of IAH, with a sensitivity and specificity of 73%. Taking this result into account, in future settings, our method might serve as a tool for the early and objective identification of IAH. However, further studies are needed to validate the time to performing a scan after reaching hypoglycaemia.

Funding sources

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No. 777460. The JU receives support from the European Union's Horizon 2020 research and innovation programme, and EFPIA and T1D Exchange, JDRF, International Diabetes Federation (IDF), The Leona M. and Harry B. Helmsley Charitable Trust.

Competing interests

O.M. has received lecture fees from Medtronic, travel grants from Novo Nordisk A/S, Novo Nordisk AT, Novo Nordisk UK, Medtronic AT, Sanofi-Aventis, research grants from Sêr Cymru II COFUND fellowship/European Union, Novo Nordisk A/S, Dexcom, Sanofi-Aventis and Novo Nordisk AT, as well as material funding from Abbott Diabetes Care. M.L.E. has received a KESS2/European Social Fund scholarship and travel grants from Novo Nordisk A/S and Sanofi-Aventis, research grants form Sanofi-Aventis and Dexcom. H.S. has received honoraria, travel support or unrestricted research grants by Amgen, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi-Aventis. H.S. has received honoraria, travel support or unrestricted research grants from Amgen, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi-Aventis. J.K.M. is a member in the advisory board of Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor SA and Sanofi, received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Eli Lilly, Dexcom, Novo Nordisk, Roche Diabetes Care, Sanofi, Servier and Takeda, and is shareholder of decide Clinical Software GmbH. The remaining authors have no relevant conflict of interest to disclose.

Acknowledgements

We want to thank the participants for the adherence to the study protocol. This study is a predefined secondary outcome analysis and is registered at the German Register for Clinical Trials (DRKS.de; DRKS00013667). This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777460. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and T1D Exchange, JDRF, International Diabetes Federation (IDF), The Leona M. and Harry B. Helmsley Charitable Trust. Data in this manuscript have been submitted as an abstract to the American Diabetes Association (ADA) conference 2020.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Time spent in glycaemic ranges in comparison of IAH vs. non-IAH (without impaired hypoglycaemia awareness) assessed by Gold score, Clarke score and Pedersen-Bjergaard score.

Table S1. Absolute numbers for the assessment of people with and without IAH in comparison of Gold score vs. Clarke score, Gold score vs. Pedersen-Bjergaard score and Pedersen-Bjergaard score vs. Clarke score.