Detection of hypoglycemia associated EEG changes during sleep in type 1 diabetes mellitus

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ABSTRACT

Objective: Nocturnal hypoglycemia is a feared complication to insulin treated diabetes. Impaired awareness of hypoglycemia (IAH) increases the risk of severe hypoglycemia. EEG changes are demonstrated during daytime hypoglycemia. In this explorative study, we test the hypothesis that specific hypoglycemia-associated EEG-changes occur during sleep and are detectable in time for the patient to take action.

Research design and methods: Ten patients with type 1 diabetes (duration 23.7 years) with IAH were exposed to insulin-induced hypoglycemia during the daytime and during sleep. EEG was recorded and analyzed real-time by an automated multi-parameter algorithm. Participants received an auditory alarm when EEG changes met a predefined threshold, and were instructed to consume a meal.

Results: Seven out of eight participants developed hypoglycemia-associated EEG changes during daytime. During sleep, nine out of ten developed EEG changes (mean BG 2.0 mmol/l). Eight were awakened by the alarm. Four corrected hypoglycemia (mean BG 2.2 mmol/l), while four (mean BG 1.9 mmol/l) received glucose infusion. Two had false alarms. EEG-changes occurred irrespective of sleep stage. Post hoc improvement indicates the possibility of earlier detection of hypoglycemia.

Conclusions: Continuous EEG monitoring and automated real-time analysis may constitute a novel technique for a hypoglycemia alarm in patients with IAH.

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1. Introduction

Hypoglycemia is a feared complication to insulin-treated Type 1 Diabetes (T1D) and is often the limiting factor for further intensification of treatment [1]. Patients with T1D have severe hypoglycemic events 1–3.2 times per year [2–4], defined as being cognitively impaired to such an extent that they need help from others to restore euglycaemia [3]. The rate increases

with increasing duration of diabetes [3] and intensified treatment [5].

Impaired awareness of hypoglycemia (IAH) is defined as a reduced or abolished ability to sense and respond to hypoglycemia, and is a predictor for risk of severe hypoglycemia [2,6]. Hypoglycemia awareness decreases with the increased duration of diabetes, tight glycemic control and recent hypoglycemic episodes [7,8]. Furthermore, hormonal counter-regulation diminishes with increased duration of diabetes [1].

The fear of hypoglycemia may prevent the patient from obtaining tight glucose control [1] which is correlated with decreased risk of mortality, cardiovascular morbidity and micro vascular disease [1,8]. A hypoglycemia alarm system might allow tighter glycemic control without increasing the risk and fear of hypoglycemia.

The characteristic properties of the electroencephalogram (EEG) during hypoglycemia include higher amplitude and lower frequency and are distinct from the normal EEG during euglycaemia [9]. About 50% of all hypoglycemic events occur during sleep at night [8]. Sleep EEG differs from that in the awake state by occurrence of slow wave patterns thus sharing some of the properties seen during hypoglycemia.

It has previously been shown that hypoglycemia-associated EEG-changes occur approximately 30 min prior to severe cognitive impairment (range 3–113 min) in the awake patient with T1D. Furthermore these changes which were recorded from a single subcutaneous electrode during daytime could be detected by an automated mathematical algorithm [10]. The hypoglycemia associated changes in the EEG have also been identified in children [11].

The aim of this study is to investigate if a real-time, computerized EEG-analyzing algorithm can detect hypoglycemia-associated EEG changes irrespective of sleep stage and, if so, might be used as an alarm system for hypoglycemia during sleep and in the awake state. Furthermore, we tested whether the alarm system can detect impending hypoglycemia in due time for the patient to take action. Since patients with IAH are the target group for a hypoglycemia device, we tested this specific group of T1D patients in the study.

2. Method and material

Ten patients with T1D were enrolled from the outpatient clinic at the Department of Endocrinology, Sydvestjysk Sygehus, Esbjerg. All participants had IAH as defined by either Gold's method [6] or a history of ≥2 severe hypoglycemic events during the last 2 years. Patients with a history of cardiovascular disease (e.g. stroke, acute myocardial infarction, limb ischemia or heart failure), epileptic seizures, structural brain damage (verified through patient charts and radiology reports), use of antiepileptic drugs or beta-blocking agents for any purposes were excluded. For each participant, the study included three visits at least 7 days apart (mean 13 days (range 7–47)). The study was approved by the local ethics committee and followed the Helsinki declaration.

Visit 1 (daytime assessment): the participants arrived in the research unit between 8 and 10 a.m. in a non-fasting state. If blood glucose (BG) was ≤4.0 mmol/l on arrival, the participants consumed 100 ml of fruit juice. Under sterile conditions and local analgesia an electrode (Foramen Electrode AD-Tech Medical (WI, USA), length 300 mm, diameter 1.1 mm with 3 contact points with a center-to-center distance of 30 mm) was inserted subcutaneously over the temporal region behind the ear. The electrode was connected to an EEG recorder (g-USBamp, G-TEC, Austria). The EEG was sampled at 512 Hz and analyzed real-time by an automated algorithm (see 'EEG-analysis' below). Prior to inducing hypoglycemia, the alarm-sound, a loud beeping noise, was demonstrated for the patient, and a juice and sandwich were placed on the bed table. Hypoglycemia was induced by infusion of 50 IU of Actrapid® (Novo Nordisk, Bagsværd, Denmark) added to 489.5 ml of 9% saline solution (Baxter NaCl isotonic) and 10 ml of the participants whole blood. The initial infusion rate depended on the BG at the start of the experiment and the infusion rate was subsequently adjusted to achieve a steady fall in plasma glucose of 1.0 mmol/l per 15 min. Venous plasma glucose was measured every 5 min by ABL-705 (Radiometer Denmark, Brønshøj, Denmark). If the participants did not respond to the hypoglycemia alarm by food ingestion, they were given intravenous glucose 20% (Baxter 200 g/l glucose) via peripheral vein catheter (initial infusion rate of 64–103 ml/min). Causes for terminating the induction of hypoglycemia were defined as one of the following: (i) alarm due to EEG changes corrected by the patient by food ingestion, (ii) the patient did not respond to the alarm within 5 min, (iii) BG level was lower than 1.5 mmol/l by two consecutive measurements, or (iv) the patient or investigator requested the experiment to stop (due to severe hypoglycemic symptoms, fear of seizures or other acute complications). At BG 6.0 mmol/l, 3.0 mmol/l, and when the experiment ended, additional blood samples were drawn for the analysis of counter-regulatory hormones. Visit 1 was performed while the patients were awake.

Visit 2 (night assessment with alarm): the patients were encouraged to stay up until late the evening before the study night and only sleep 4–5 h to ensure that they could sleep during the study night. The patients met at the hospital between 9 and 11 p.m. The study procedures were identical to those of visit 1 with the following exceptions: the participants were placed in a bed in a separate room with a dim light to allow the investigator to observe the patient. In addition to the subcutaneous electrode, a full 10/20 electrode montage and electrodes for electromyography, electrooculography and electrocardiography were placed. Induction of hypoglycemia started when the patients had shown clinical signs of sleep for at least 1 h. Causes for termination of hypoglycemia were identical to the daytime assessment and, if necessary, glucose was infused until the patient recovered from symptoms of hypoglycemia. Afterwards, the patient was allowed to sleep until the next morning.
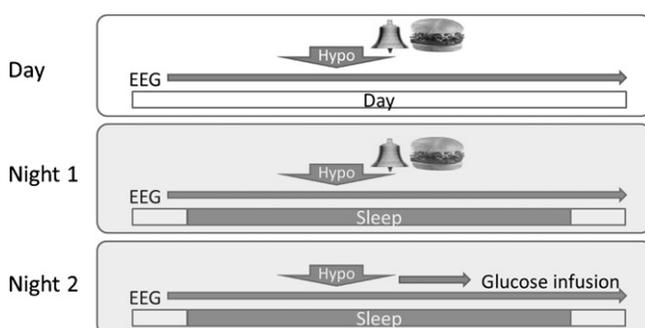
Visit 3 (night assessment without alarm): the purpose of this visit was to ensure that all the participants experienced hypoglycemia. The study procedures were identical to those of visit 2 with one exception: the patient did not receive an alarm when the hypoglycemia-induced EEG-changes exceeded the threshold value. The causes of termination were the same as for the daytime assessment, except for the alarm.

EEG analysis: the development of the algorithm for automated quantitative EEG analysis has previously been

described [10]. Briefly, the original algorithm was developed on the basis of six patients with T1D exposed to insulin-induced hypoglycemia during continuous EEG recording. One-second EEG epochs were manually scored as consistent or not consistent with the presence of hypoglycemia. Based on the Bayesian learning principle and a set frequency-dependent power estimates, a classical two layer neural network was trained to model the neurophysiologist's ability to detect epochs consistent with impending hypoglycemia. The resulting multi-parameter algorithm would declare an event, when an incoming epoch was interpreted as associated with hypoglycemia changes. A number of declared events within a predefined time window would trigger a hypoglycemia alarm. This is implemented by integrating 1's for every event, ultimately declaring an alarm when a predefined threshold has been exceeded.

Before initiation of the present study, a pilot experiment was conducted in eight patients with T1D exposed to insulin-induced hypoglycemia during sleep. The patients that participated in these pilot studies did not participate in the current trial, but were recruited according to the same inclusion and exclusion criteria. Data from the pilot studies were used to optimize the original algorithm and ensure an appropriate balance between sensitivity and specificity during sleep (night algorithm 1). Since this was an explorative study, we performed further optimization based on the data from the first five patients to further increase the sensitivity of the alarm (night algorithm 2) and the predefined thresholds were lowered, enabling detection of a larger proportion of the recorded hypoglycemia events post-analytically. In both the day and night experiments the threshold for hypoglycemia alarm was predefined. False alarms were defined as EEG-changes above the threshold value when BG was above 3.5 mmol/l. Fig. 1 shows an overview of the study design.

Sleep scoring was performed twice, by two experts (PJ and MDG). The EEGs were independently scored and PJ and MDG were blinded for the blood glucose value or the timing of hypoglycemia. The EEG recordings were scored according to

international standards (The Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, American Academy of Sleep Medicine (AASM), 2007) [12]. In case of discrepancy between the two observers, the EEG was reassessed and agreement achieved for a final scoring. Sleep stages were noted at 5 min before detected hypoglycemia, at hypoglycemia and when the curve of integrated events of hypoglycemia started decrease as an indication of restored euglycaemia. Fig. 2 shows an example of EEG-changes during a night experiment.

2.1. Patient characteristics

We studied ten participants (7 males and 3 females) with T1D of which one patient decided to leave the study after the first night experiment. They were 47 ± 6.7 (mean $\pm$ SD) years of age and the duration of diabetes was 23.7 years [range 10–37 years]. Their HbA_{1c} was 7.5% [range 5.6–9.0] (mean 58 mmol/mol [range 30–75 mmol/mol]). None had micro- or macro-albuminuria, three had diabetic neuropathy, and three had background retinopathy.
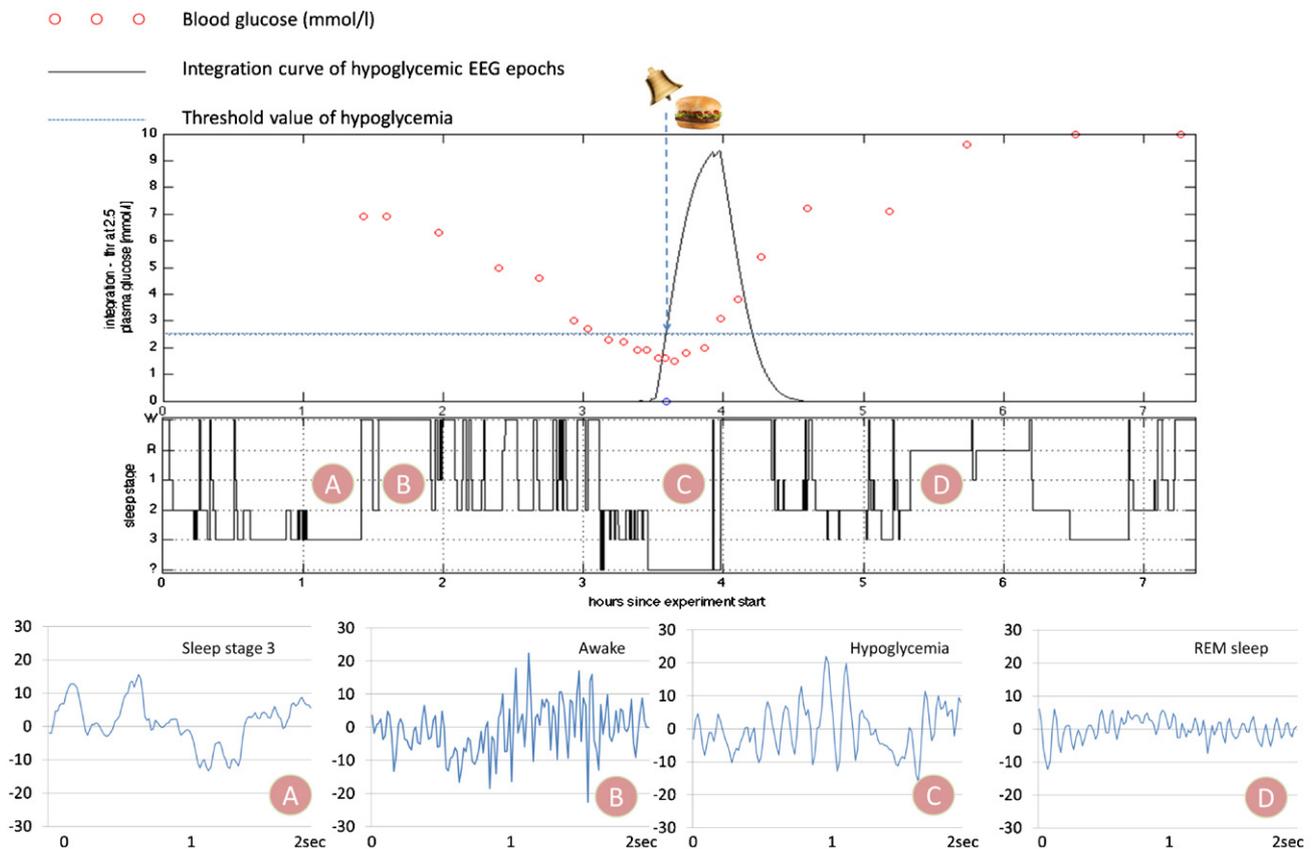
3. Results

3.1. Hypoglycemia alarms

Daytime assessment, visit 1: of the nine patients who completed the daytime visit, six (67%) received an alarm and reacted adequately by carbohydrate intake thereby correcting the hypoglycemia. One patient (11%) received an alarm, but was unable to respond adequately due to cognitive impairment, and two patients (22%) did not receive an alarm. Accordingly the hypoglycemia was terminated by glucose infusion in these three participants. Their blood glucose levels were 2.4 mmol/l, 1.8 mmol/l and 2.8 mmol/l at the time of glucose infusion.

Night assessment with alarm, visit 2: all ten patients completed the first night assessment. The first five patients (50%) were analyzed by night algorithm 1. Of these patients one (20%) received an alarm and reacted adequately by carbohydrate intake. Three patients (60%) received an alarm, but did not react adequately and received intravenous glucose to restore euglycaemia. The last patient (20%) did not receive an alarm and the experiment was stopped due to a low blood glucose level (1.6 mmol/l), profuse sweating and tachypnea. Of the other five patients where night algorithm 2 was applied, three patients (60%) received an alarm and reacted accordingly. One patient (20%) misinterpreted the alarm beep as being an alarm from the intravenous pump (blood glucose 2.0 mmol/l at alarm), and the last patient (20%) received the alarm when blood glucose was 1.6 mmol/l. He reacted to the alarm, but needed to be reminded to eat and drink to restore normal blood glucose level.

Night assessment without alarm, visit 3: nine participants completed the second night trial. Hypoglycemia-associated EEG changes exceeding the predefined threshold were seen in three (75%) out of four patients using algorithm 1 and four (80%) out of five using algorithm 2.

There were in total two false positive alarms during the total of approximately 130 h of EEG data. One false alarm

Fig. 1 – Study design.
Each patient underwent three study sessions. During daytime and the first night session the patients received an auditory alarm when EEG-changes exceeded a predefined threshold. A sandwich and juice were available for the patient, but no instructions were given during the hypoglycemic episode. If the patient did not react hypoglycemia was ceased by glucose infusion. For further information see Section 2.

Fig. 2 – Typical EEG-changes during a night experiment.
Representative example of a successful night 1 experiment: the bell illustrates the alarm and the hamburger illustrates the meal. The upper panel shows the blood glucose profile and the curve for integrated EEG-events of hypoglycemia. The integration curve rose steeply following hypoglycemia. The patient received an alarm at blood glucose 1.8 mmol/l, where the integration curve crossed the threshold. Blood glucose increased following ingestion of the meal, and the integration curve normalized accordingly. The middle panel shows the sleep stage according to the AASM scoring. As seen the patient ran through all stages of sleep during the night. After a short period of wakefulness the patient went back to sleep. The lower panels show epochs of representative EEG during wakefulness (B), REM sleep (D), stage 3 sleep (A) and hypoglycemia (B).

occurred during the day, one during night 1 and one during night 2 using algorithm 1. There were no false positive alarms during the 60 h using algorithm 2.

The EEG recordings were exposed to post hoc analysis. For the post hoc analysis a longer-term normalization was performed using EEG data from the entire night, thus allowing the algorithm to learn the individual variations in the participant EEG. This facilitated a more individual adjustment of the algorithm. Using this procedure, all participants had hypoglycemic changes and in addition the alarm would have appeared 3–6 min earlier.

Table 1 summarizes the results regarding alarms during the three visits.

3.2. Counter-regulatory hormones

Blood for measurement of counter-regulatory hormones was drawn when BG was 6 mmol/l, 3 mmol/l and at the end of the experiments. All participants were glucagon non-responders. We saw an increase in adrenaline, noradrenalin, human growth hormone and cortisol, when participants were maximally hypoglycemic.

Results of analysis of the counter-regulatory hormones are shown in Fig. 3.

3.3. Hypoglycemia and sleep

Sleep efficiency was 67% (range 45–86%) during the night experiment. According to the AASM scoring participants spent 17% of nighttime in sleep stage N1, 49% in sleep stage N2, 25% in sleep stage N3 and 10% in REM sleep. All participants did go through stage N3 sleep during both nights. Five minutes before the occurrence of hypoglycemia, 11% of the participants were in sleep stage N1, 53% in sleep stage N2, 18% in sleep stage N3, and 17% were awake. Prior to the induction of hypoglycemia, the participants were all clinically sleeping.

4. Discussion

Long duration of diabetes, recent episodes of hypoglycemia and sleep all tend to compromise physiological (defective glucose counter-regulation) and behavioral (IAH) defenses against hypoglycemia. Both severe hypoglycemia and

Table 1 – Results.					
	Day	Night 1 – algorithm 1	Night 2 – algorithm 1	Night 1 – algorithm 2	Night 2 – algorithm 2
Number of participants	9	5	4	5	5
Alarm, able to correct blood glucose levels (number of patients)	6	1	NA	3	NA
Alarm, not able to correct blood glucose levels (number of patients)	1	3	NA	2	NA
No alarm (number of patients)	2	1	NA	0	NA
False alarm (defined as blood glucose above 3.5 mmol/l) (number of patients)	1	1	NA	0	NA
Blood glucose at the time of the alarm (mean (range)) mmol/l	2.7 (1.5–4.9)	2.5 (1.5–3.4)	NA	2.5 (1.5–3.4)	NA

The table shows the main results of the study. Ten participants participated in the experiment. Nine participants completed both a daytime experiment and two nighttime experiments, while one patient dropped out after the first night experiment. During the night trials, the first five participants were monitored using night algorithm 1 and the remaining five using night algorithm 2. For each patient the same algorithm was used for both night visits.

non-severe hypoglycemia are significantly more frequent in patients with IAH and nocturnal biochemical hypoglycemia occurs in 40–50% of unselected patients with T1D as assessed by short-term continuous glucose monitoring (CGM) [13]. Not only does this result in an increased risk of medical emergencies, it also contributes to the vicious cycle of hypoglycemia-associated autonomic failure [7]. In addition, events of severe hypoglycemia are the most important predictor for future hypoglycemia [14].

Hypoglycemia induced EEG changes have been demonstrated by many groups [9,15–17]. We have recently confirmed the presence of specific EEG changes preceding neuroglyco-penic manifestations in patients with T1D exposed to insulin-induced hypoglycemia [10]. In the present paper, we further explore the possibility to base a nocturnal hypoglycemia alarm on a continuous EEG recording.

To the best of our knowledge, this is the first study to examine the potential of a continuous EEG monitoring system
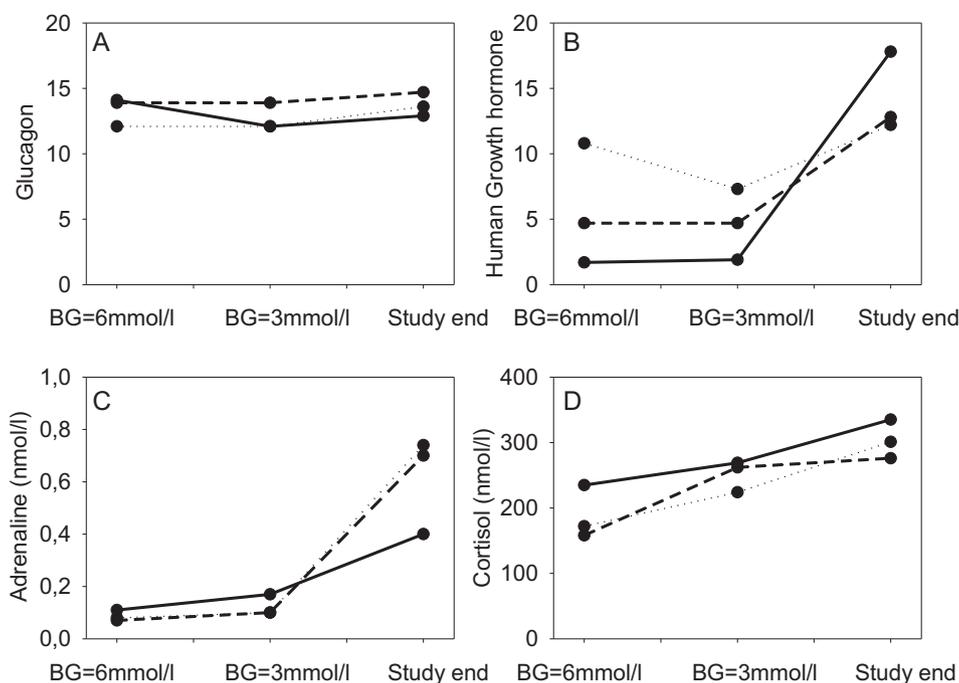
Fig. 3 – Counter regulatory hormones.
Panels A–D show the response in four counter regulatory hormones (glucagon, human growth hormone, adrenaline and cortisol). All measurements were done at blood glucose levels prior to hypoglycemia, during hypoglycemia and at the end of the experiment (defined as either at the sounding of the alarm or by investigator intervention). The measurements are shown as the mean value of the hormone. The solid line represents the experiment. The dotted line represents the night 1 experiment and the scratched line (—) represents the night 2 experiment.

with real-time analysis to serve as a hypoglycemia alarm. A recent study evaluated the applicability of an electrocardiography-based hypoglycemia alarm during spontaneous hypoglycemia [18]. The sensitivity and specificity were both found to be approximately 70% in an in-hospital setting. This device has not been tested in long-term trials and is not commercially available. It underscores, however, that bio-sensors (i.e. devices that combine a biological component with a physicochemical detector component) may constitute a supplementary approach to interstitial glucose measuring (e.g. CGM) in the attempt to develop hypoglycemia alarm devices and may in turn become an integrated part of a closed-loop system.

We found that participants with T1D complicated by IAH and lack of counter-regulatory hormone release consistently display EEG-changes compatible with hypoglycemia irrespective of sleep stage. Earlier studies hypothesized that only patients with absent glucagon response have hypoglycemia-associated EEG changes during sleep [17]. In our study, all participants lacked glucagon response both in a waking state and during sleeping. However the hormone response (hGh, cortisol and adrenaline) during the night experiments might have been even higher if the patients have had a less disturbed sleep than was allowed due to study conditions. The hypoglycemia associated changes are sufficiently specific to be distinguished from daytime and sleep EEG patterns by a general automated algorithm. In most cases, the patient woke up as a result of the alarm. In some cases, however, the patient was unable to react to the alarm and glucose supplementation was required. The algorithm used was based on the previously described daytime algorithm with an initial modification based on the pilot night experiments. We wanted to test the applicability of the EEG-based alarm in a nighttime sleep setting and, to record EEG during concomitant sleep and hypoglycemia for further optimization of the algorithm. Post hoc adjustments of the algorithm improved the sensitivity of the alarm. If the optimized algorithm had been used, the participants would have received the alarm on average 6 min earlier during the nighttime experiments. The optimized algorithm will be tested in a large-scale clinical trial.

CGM is likely to become an integrated part of a closed-loop artificial pancreas. The monitors are consistently being improved with optimized technology and incorporation of multiple parameter prediction algorithms [19]. In larger clinical trials, the use of CGM has been shown to improve glycemic control in certain patients groups [20,21]. However, the frequency of severe hypoglycemia is not significantly reduced by CGM [20–22]. It must be emphasized, however, that these studies were not powered to address this issue. A reduced usage of the device over time may contribute to this finding. In fact, at the end of a six-month study, the device was only used 35–70% of the time depending on age group [21,22]. This reason for this is not discussed in the paper, but may relate to inconvenience for the user, the need for repeated calibration or unwillingness to change catheters.

It can be questioned if the present study, performed in an in-hospital setting, mirrors the everyday situation. During the night experiments the participants slept on average 67% of the time and all participants experienced stage N1, N2 and N3 sleep (in 17%, 49% and 25% of the time respectively), which is less time spent in deep sleep than expected [12]. The quality of sleep is likely to be affected by frequent blood glucose measurements and the dim light in the laboratory allowing the investigators to observe the participants. Importantly, hypoglycemia was detected in all sleep stages with the exception of REM-sleep, which was present in only 10% of the time. This indicates that hypoglycemia-associated EEG changes overrule normal sleep patterns irrespective of sleep stage and that an alarm device potentially can encompass the entire night. We aimed to achieve hypoglycemia by a steady decrease in blood glucose of approximately 1 mmol/l per 15 min. During normal conditions, this rate may be faster or slower depending on insulin dose and timing, recent physical activity and insulin sensitivity. In a previous study, we found no significant association between the rate of decline in blood glucose and the timing of EEG changes [10]. A very fast decline in blood glucose may, on the other hand, reduce the time from EEG changes to cognitive decline. Whether this will result in missed alarms will be tested in a future study with concomitant CGM and EEG based hypoglycemia alarm.

In conclusion, this study establishes that it may be possible to prevent events of severe nocturnal hypoglycemia by using continuous EEG monitoring and real-time automated data analysis in patients with T1D. We found that some participants received no alarm prior to severe hypoglycemia. Post hoc analysis of the EEGs has shown hypoglycemia-associated EEG changes prior to hypoglycemia in all the participants. This indicates that further refinement of the algorithm will improve the sensitivity of the alarm.

Author contributions

LF included the patients into the study, collected the data and wrote the manuscript. LSS collected the data and wrote the manuscript. PJ analyzed the EEG data and reviewed/edited manuscript. MDG analyzed the EEG data and reviewed/edited manuscript. RE researched data and reviewed/edited manuscript. LSR researched data and reviewed/edited manuscript. CJ designed the study and wrote the manuscript. HBN designed the study and reviewed/edited manuscript. BT reviewed/edited manuscript. LF and LSS share the first author status of this article.

Conflict of interests

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