Effects of continuous glucose monitor-recorded nocturnal hypoglycaemia on quality of life and mood during daily life in type 1 diabetes

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Abstract

Aims/hypothesis The aim of this work was to assess the effect of spontaneous nocturnal hypoglycaemia on quality of life and mood during subsequent days in type 1 diabetes.

Methods A total of 153 people with type 1 diabetes participated in 6 days of blinded continuous glucose monitoring while documenting hypoglycaemic symptoms, quality of life and mood, daily. Hypoglycaemia was defined by interstitial glucose ≤ 3.9 mmol/l ($IG_{3.9}$) and ≤ 3.0 mmol/l ($IG_{3.0}$) for ≥ 15 min and was classified as asymptomatic if no hypoglycaemic symptoms were reported.

Results Self-estimated quality of life assessed by the EQ-5D VAS (but not by the WHO Well-Being Index) was higher the day after asymptomatic (but not after symptomatic) hypoglycaemic nights, as compared with non-hypoglycaemic nights ($IG_{3.9}$, $p = 0.021$; $IG_{3.0}$, $p = 0.048$). The effect increased with lower glucose nadir and longer duration of nocturnal hypoglycaemia ($IG_{3.9}$, $p = 0.03$). The finding was confined to participants with impaired hypoglycaemia awareness. There was no effect of nocturnal hypoglycaemia on mood or self-estimated effectiveness at work the following day.

Conclusions/interpretation Individuals with type 1 diabetes and impaired hypoglycaemia awareness reported higher quality of life on days preceded by nights with asymptomatic (but not symptomatic) hypoglycaemia. The effect was amplified by lower glucose nadir and longer duration of the episodes and may help explain resistance to implementation of interventions to reduce hypoglycaemia in many people with impaired hypoglycaemia awareness.

Keywords Hypoglycaemia · Hypoglycaemia awareness · Impaired awareness · Quality of life · Type 1 diabetes

Abbreviations

CGM	Continuous glucose monitoring
EQ-5D VAS	EuroQol-5D visual analogue scale
$IG_{3.0}$	Interstitial glucose ≤ 3.0 mmol/l
$IG_{3.9}$	Interstitial glucose ≤ 3.9 mmol/l
QoL	Quality of life
SMBG	Self-monitoring of blood glucose
TIR	Time in range

UWIST University of Wales Institute of
Science and Technology

Introduction

The experience of hypoglycaemia is generally believed to affect people with diabetes in a negative manner [1, 2]. Thus, several retrospective studies demonstrate that self-reported hypoglycaemia is associated with poorer quality of life (QoL) in type 1 diabetes [1, 3–5], an effect amplified by the frequency and severity of the hypoglycaemic episodes [3, 5, 6]. Nocturnal experimental hypoglycaemia is shown to reduce QoL the following day [7]. A few survey studies compare the effect of nocturnal vs daytime hypoglycaemic events on QoL and find that people with self-reported nocturnal mild hypoglycaemia report poorer QoL compared with those reporting daytime hypoglycaemia [3, 5].

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Research in context

What is already known about this subject?

- Symptomatic hypoglycaemia has profound biological and psychological effects on people with diabetes
- Neuroimaging studies show different brain activation patterns in people with normal and impaired hypoglycaemia awareness
- Little is known about the impact of nocturnal hypoglycaemia (particularly asymptomatic hypoglycaemia) on day-to-day quality of life in type 1 diabetes

What is the key question?

- Does preceding spontaneous nocturnal hypoglycaemia impact day-to-day quality of life and mood in individuals with type 1 diabetes and, if so, does hypoglycaemia awareness influence this?

What are the new findings?

- Quality of life is improved the day following a night with asymptomatic hypoglycaemia in people with type 1 diabetes and impaired hypoglycaemia awareness
- The effect is incremental for both lower glucose nadir and longer duration of the hypoglycaemic episode

How might this impact on clinical practice in the foreseeable future?

- The findings demonstrate a potentially complex interplay between biological and psychological effects of hypoglycaemia, which may result in differences in perceptions of, and attitudes towards, hypoglycaemia among people with diabetes. It is important to acknowledge these factors when designing and implementing interventions to prevent hypoglycaemia

Also, mood may be affected by hypoglycaemia in type 1 diabetes. A prospective study shows that people with severe hypoglycaemia chronically have a higher level of anxiety and depression compared with people without severe hypoglycaemia but no acute effects of the episodes per se [8]. Other studies explore the consequences of symptomatic mild hypoglycaemia on mood in type 1 diabetes [9, 10] and find that mood shifts towards unhappiness and a less energetic and tense state [9, 10].

Previous research mainly focuses on the consequences of symptomatic hypoglycaemia, which, on one hand, may be a product of biological effects of hypoglycaemia on the brain and, on the other hand, may be psychological effects arising from the participants' knowledge of the episodes. Little is known about the impact of asymptomatic hypoglycaemia. Since the majority of hypoglycaemic episodes in type 1 diabetes are asymptomatic [11, 12], these episodes may potentially have a major impact on QoL, mood and effectiveness during daily life.

Studies applying advanced neuroimaging modalities to assess the effect of hypoglycaemia on brain function show that people with impaired awareness of hypoglycaemia may react differently to hypoglycaemia compared with people with normal hypoglycaemia awareness [13, 14], suggesting diverse biological effects of hypoglycaemia.

The aim of this study was to investigate the impact of preceding spontaneous nocturnal hypoglycaemia (asymptomatic, in particular) on QoL, mood and effectiveness during the

following days in type 1 diabetes. Furthermore, we aimed to explore potential differences in QoL responses according to state of hypoglycaemia awareness.

Methods

The study was a prospective observational study approved by the Danish Data Protection Agency and the Regional Committee on Biomedical Research Ethics (H-15002715). Written informed consent was obtained from all participants. A detailed description of the study design has been published previously [12].

Participants

A total of 153 adults (≥ 18 years old) with type 1 diabetes duration of at least 1 year were recruited consecutively in the outpatient clinic at Nordsjællands Hospital Hillerød, Denmark. Individuals with concomitant malignant disease or end-stage renal disease, or those who were pregnant, were excluded from the study. The baseline characteristics of the participants are shown in Table 1.

Study design

Following recording of baseline characteristics and blood sampling, the participants underwent 6–7 days of blinded

Table 1 Characteristics of participants with type 1 diabetes

Characteristic	Value
<i>N</i>	153
Male sex, <i>n</i> (%)	90 (59)
Age, years	52 ± 14
Duration of diabetes, years	22 ± 15
C-peptide negative, <i>n</i> (%) ^a	108 (71)
BMI, kg/m ²	26 ± 4
Total insulin dose, U/day	47 ± 22
Insulin therapy, <i>n</i> (%)	
Analogue	123 (80.4)
Analogue/human	22 (14.4)
Human	8 (5.2)
Insulin treatment regimen, <i>n</i> (%)	
1–3 daily injections	6 (4)
≥ 4 daily injections	117 (76)
CSII	30 (20)
HbA _{1c}	
mmol/mol	64 ± 12
%	8.0 ± 1.1
Hypoglycaemia awareness classification, <i>n</i> (%)	
Gold [16]	
Aware	121 (79)
Reduced awareness	31 (20)
Clarke [17]	
Aware	106 (69)
Unclassified	20 (13)
Reduced awareness	22 (14)
Hillerød [18]	
Aware	71 (46)
Impaired awareness	59 (39)
Unaware	22 (14)
Episodes of severe hypoglycaemia (per person, over previous year)	0.3 ± 1.0; 0 (0–8)
Episodes of mild symptomatic hypoglycaemia (per person, over previous week)	1.9 ± 2.5; 1 (0–16)

Values are mean ± SD or median (range), unless indicated otherwise

^a C-peptide <20 pmol/l was undetectable

CSII, continuous subcutaneous insulin infusion

continuous glucose monitoring (CGM), while they continued their usual daily activities and treatments. During the monitoring period, the participants documented episodes of symptomatic hypoglycaemia (≤ 3.9 mmol/l). Daily activities, food intake and insulin dosing were recorded every half hour in a diary. A detailed questionnaire was filled in by the participants regarding each episode of hypoglycaemia, including whether they had symptoms or not.

The device used for CGM was blinded iPro 2 with Enlite Glucose sensors (Medtronic MiniMed, Northridge, CA, USA), which has a reported overall mean absolute relative

difference (MARD) of 13.9% and 18.4% in the hypoglycaemic range (glucose level ≤ 3.9 mmol/l), a sensitivity of 90.1% and a positive predictive value of 83.8% for hypoglycaemia [15]. Calibration was performed according to the manufacturer's recommendations (four times daily) with blood glucose meter measurements (Contour XT meter using Contour NEXT test strips; Bayer, Basel, Switzerland).

Questionnaires

At entry into the study, the participants filled in questionnaires regarding self-estimated state of hypoglycaemia awareness according to three validated methods: Gold [16]; Clarke [17]; and Hillerød [18]. Furthermore, the questionnaire asked the participant to state the number of episodes of severe hypoglycaemia experienced in the preceding year. Severe hypoglycaemia was defined as an episode where assistance from another person was needed to restore glucose levels to normal [2]. History of diabetes, treatments (medications, use of technologies) and late diabetic complications were collected from the participants' medical records or asked for as appropriate. HbA_{1c} and C-peptide levels were measured (participants with undetectable levels (<20 pmol/l) were categorised as C-peptide negative).

Every evening participants filled in questionnaires regarding QoL, mood and self-estimated effectiveness at work. QoL was assessed by the WHO-5 Well-Being Index [19] and the EuroQol-5D visual analogue scale (EQ-5D VAS) [20]. In both questionnaires, the participants score between 0 and 100, with higher scores indicating higher QoL. A difference in score of ≥ 7 on the EQ-5D VAS is reported to be a clinically important change in QoL [21]. Changes in mood were evaluated by the University of Wales Institute of Science and Technology (UWIST) Mood Adjective Checklist [22]. This checklist describes three main mood states: energetic arousal (feeling active rather than tired); tense arousal (feeling anxious vs relaxed); and hedonic tone (feeling happy vs sad). Self-estimated effectiveness at work was assessed hourly using a Likert-type visual analogue scale of 1 (not effective) to 7 (very effective).

CGM analysis

An episode of hypoglycaemia was classified as an episode with continuous interstitial glucose values below two threshold levels: interstitial glucose ≤ 3.9 mmol/l (IG_{3.9}), as formerly recommended by the ADA; and interstitial glucose ≤ 3.0 mmol/l (IG_{3.0}), as suggested by the International Hypoglycaemia Study Group and endorsed by ADA and the EASD [2, 23–25]. A valid hypoglycaemic event was defined by glucose values below the thresholds for ≥ 15 min, and recovery from hypoglycaemia was defined as interstitial glucose values continuously above the threshold for

≥ 20 min [23, 24, 26]. An episode of hypoglycaemia without self-reported symptoms of hypoglycaemia in the diary was classified as asymptomatic. The hypoglycaemic nadir of an episode was defined as the lowest interstitial glucose value during the episode. Night-time was defined as 11:00 hours to 07:00 hours. To assess whether daytime and night-time hyperglycaemia had an effect on QoL, an episode of significant hyperglycaemia was defined as glucose levels continuously >14 mmol/l for ≥ 15 min [23, 24]. Time in range (TIR) was defined as the percentage of time spent with a glucose level 4–10 mmol/l [23, 24].

Statistical analysis

A total of 153 patients were included but QoL data were not reported for two patients and awareness status was unknown for one patient, so n ranged from 150 to 153 in analyses. This study was an explorative study, so no power calculations could be made. We used standard descriptive statistics to characterise participants. Median and range are presented in addition to mean $\pm$ SD, when distribution of data is skewed. The Mixed Models analysis was used to investigate the effect of prior nocturnal hypoglycaemia on QoL, mood and effectiveness the day after. The Mixed Models analysis enables adjustment for correlation due to repeated observations (i.e. 6 days of CGM) on each participant. For categorical variables, the resulting estimate (i.e. increase or decrease in scores on the questionnaires) and p values indicate comparison of nights without hypoglycaemia vs hypoglycaemic nights (reference: non-hypoglycaemic nights). For quantitative variables, the estimate and p values indicate the increase per increment of the variable. The following variables were included in the model: episode of hypoglycaemia the preceding night (present or not) and duration of hypoglycaemic episodes (per 15 min increment [i.e. the shortest duration of a hypoglycaemic episode]). All variables were assessed in total as well as separated into asymptomatic and symptomatic nocturnal hypoglycaemia. To assess the influence of possible confounders we also included the following variables in the model: TIR (daytime); episode of daytime hyperglycaemia (present or not); episode of nocturnal hyperglycaemia (present or not); fasting morning self-monitoring of blood glucose (SMBG), categorised into three groups (hypoglycaemic morning SMBG ≤ 3.9 mmol/l [SMBG $_{\leq 3.9}$], morning SMBG in range [SMBG $_{4-10}$; glucose levels of 4–10 mmol/l] and hyperglycaemic morning SMBG >10 mmol/l [SMBG $_{>10}$]); and HbA $_{1c}$. Non-parametric tests were used to compare daytime glycaemic variables on days with and without prior nocturnal hypoglycaemia.

Analyses were performed with SPSS software package (version 25.0; IBM, Armonk, NY, USA), and a p value <0.05 (two-sided) was chosen as level of statistical significance.

Results

Occurrence of nocturnal hypoglycaemia

The 153 participants were monitored for a total of 1040 days and nights, resulting in 6.1 ± 0.9 (mean $\pm$ SD) days and nights per person of valid recording of CGM (total duration minus periods of time with failure to record [0.5% of the total recording duration]). During the study, 54% of the participants had one or more nights with hypoglycaemia. There was at least one episode of nocturnal hypoglycaemia at threshold IG $_{3.9}$ in 141 nights (14%), and at threshold IG $_{3.0}$ in 83 nights (8%). Asymptomatic nocturnal hypoglycaemia occurred in 102 nights (10%) at threshold IG $_{3.9}$ and in 60 nights (6%) at threshold IG $_{3.0}$. Symptomatic nocturnal hypoglycaemic episodes occurred at IG $_{3.9}$ in 40 nights (4%) and at IG $_{3.0}$ in 24 nights (2%). The duration of nocturnal hypoglycaemic episodes (mean $\pm$ SD) was 181 ± 120 min (median [range], 150 [20–535] min) at IG $_{3.9}$, and 147 ± 107 min (median [range], 125 [20–450] min) at IG $_{3.0}$. The duration of asymptomatic hypoglycaemic episodes was 192 ± 122 min (median [range], 173 [20–535] min) at IG $_{3.9}$, and 160 ± 109 min (median [range], 140 [20–450] min) at IG $_{3.0}$. The duration of symptomatic episodes was 158 ± 119 min (median [range], 115 [20–465] min) at IG $_{3.9}$, and 127 ± 117 min (median [range], 76 [20–450] min) and IG $_{3.0}$.

QoL following nocturnal hypoglycaemia

EQ-5D VAS The participants reported significantly higher self-estimated QoL, indicated by higher scores on the EQ-5D VAS, after hypoglycaemic nights as compared with after non-hypoglycaemic nights when analysed at both threshold IG $_{3.9}$ and threshold IG $_{3.0}$ (Table 2). The effect size on QoL increased with decreasing hypoglycaemic levels. However, hypoglycaemic nights with glucose measurements between 3.0 and 3.9 mmol/l did not have a significant effect on QoL the following day (score difference: 1.9 [95% CI -0.88 , 4.6], $p=0.18$). The effect on EQ-5D VAS increased with longer total duration of nocturnal hypoglycaemia (score increase per 15 min increment in hypoglycaemic duration: 0.14 [95% CI 0.01, 0.27], $p=0.032$, for IG $_{3.9}$; and 0.23 [95% CI 0.02, 0.44], $p=0.030$, for IG $_{3.0}$). However, the duration of episodes with glucose measurements between 3.0 and 3.9 mmol/l did not influence EQ-5D VAS (0.07 [95% CI -0.20 , 0.34], $p=0.55$). The effect of nocturnal hypoglycaemia on EQ-5D VAS was limited to the day following the event, as no association was present on the second day following the event ($p=0.59$).

Separate analysis of nights with asymptomatic or symptomatic hypoglycaemia showed that the association was present after nights with asymptomatic hypoglycaemia (Table 2). In contrast, there was no difference in QoL following nights with symptomatic hypoglycaemia compared with nights

Table 2 QoL (assessed by the EQ-5D VAS and by the WHO-5 Well-Being Index) following overall, asymptomatic and symptomatic nocturnal hypoglycaemia at thresholds IG_{3,9} and IG_{3,0} in participants with type 1 diabetes

Hypoglycaemia status	EQ-5D VAS		WHO-5 Well-Being Index	
	Mean scores (95% CI)	<i>p</i> ^a	Mean scores (95% CI)	<i>p</i> ^a
Overall				
IG _{3,9}		0.027		0.494
NH	83.0 (80.3, 85.8)		71.1 (68.7, 75.5)	
Non-NH	80.9 (78.7, 83.1)		71.2 (68.7, 73.7)	
IG _{3,0}		0.013		0.170
NH	84.0 (80.9, 87.2)		73.5 (69.5, 77.5)	
Non-NH	80.9 (78.7, 83.2)		71.1 (68.6, 73.6)	
Asymptomatic				
IG _{3,9}		0.021		0.575
NH	83.5 (80.5, 86.5)		72.1 (68.4, 75.9)	
Non-NH	80.9 (78.7, 83.1)		71.2 (68.7, 73.7)	
IG _{3,0}		0.048		0.401
NH	83.9 (80.4, 87.4)		72.9 (68.4, 77.4)	
Non-NH	81.0 (78.8, 83.2)		71.2 (68.7, 73.7)	
Symptomatic				
IG _{3,9}		0.794		0.698
NH	81.6 (77.6, 85.7)		72.3 (66.7, 77.8)	
Non-NH	81.2 (78.9, 83.4)		71.3 (68.8, 73.8)	
IG _{3,0}		0.144		0.220
NH	84.3 (79.6, 89.0)		74.9 (68.7, 81.1)	
Non-NH	81.1 (78.9, 83.3)		71.2 (68.7, 73.7)	

^a*p* values indicate comparison of nights without hypoglycaemia vs hypoglycaemic nights (reference: non-hypoglycaemic nights), assessed via Mixed Models analysis

NH, hypoglycaemic night; non-NH, non-hypoglycaemic night

without. The duration of asymptomatic nocturnal hypoglycaemia was positively associated with scores on EQ-5D VAS; participants at threshold IG_{3,9} scored 0.16 (95% CI 0.02, 0.31) higher ($p=0.030$) on the EQ-5D VAS per 15 min increment in duration of preceding nocturnal hypoglycaemia. The same result was found at threshold IG_{3,0}, with a score of 0.27 (95% CI 0.04, 0.51) higher ($p=0.022$) per 15 min increment in duration of preceding nocturnal hypoglycaemia. The duration of symptomatic nocturnal hypoglycaemia was not associated with QoL ($p=0.84$ for IG_{3,9}; $p=0.80$ for IG_{3,0}). Neither the duration of asymptomatic nor symptomatic nocturnal events with glucose measurements solely between 3.0 mmol/l and 3.9 mmol/l was associated with scores on the ED-5D VAS ($p=0.70$ and $p=0.05$, respectively).

WHO-5 Well-Being Index Neither previous nocturnal hypoglycaemia (IG_{3,9}, $p=0.49$; IG_{3,0}, $p=0.17$) (Table 2) nor the total duration of hypoglycaemia (IG_{3,9}, $p=0.55$; IG_{3,0}, $p=0.53$) were associated with QoL assessed by the WHO-5 Well-Being Index the subsequent day. Scores on the individual questions on the WHO Well-Being Index were not associated with

prior nocturnal hypoglycaemia, including the question regarding quality of sleep (all $p>0.05$).

Mood following nocturnal hypoglycaemia

All three mood states of the UWIST Mood Adjective Checklist scored similarly on days after hypoglycaemic nights and nights without hypoglycaemia (all $p>0.05$). Likewise, the duration of hypoglycaemic nocturnal episodes was not associated with the mood the subsequent day. The results were similar at both threshold levels of hypoglycaemia (IG_{3,9} and IG_{3,0}).

Effectiveness at work following nocturnal hypoglycaemia

Participants' self-estimated effectiveness at work the day following a night with a hypoglycaemic event did not differ from the effectiveness on days after nights without hypoglycaemia (IG_{3,9}, $p=0.75$; IG_{3,0}, $p=0.12$). Furthermore, the duration of hypoglycaemic episodes (IG_{3,9}, $p=0.43$; IG_{3,0}, $p=0.07$) did not correlate to the participants' self-estimated effectiveness.

State of awareness and QoL following nocturnal hypoglycaemia

Overall QoL assessed by the EQ-5D VAS (i.e. independent of occurrence of preceding nocturnal hypoglycaemia) decreased with decreasing state of hypoglycaemia awareness (EQ-5D VAS scores [mean $\pm$ SD]: normal awareness, 82.3 ± 15.3 ; impaired awareness, 80.9 ± 16.6 ; unawareness, 76.9 ± 16.7 ; $p = 0.001$). Participants with normal awareness assessed by the Hillerød method [18] had similar scores on the EQ-5D VAS following asymptomatic hypoglycaemic nights and non-hypoglycaemic nights (Table 3, Fig. 1). Participants with impaired awareness or unawareness (as characterised by the Hillerød method) scored 3.0 (95% CI 0.5, 5.5) higher on the EQ-5D VAS at IG_{3,9} ($p = 0.017$) for nights with vs without hypoglycaemia; the difference increased to 4.8 (95% CI 1.7, 7.9; $p = 0.003$) at IG_{3,0}. Limiting the analysis to participants with hypoglycaemia unawareness according to the Hillerød method showed 10.4 (IG_{3,0} [95% CI 2.6, 18.1]) higher scores ($p = 0.014$) on the EQ-5D VAS the day following a hypoglycaemic asymptomatic night as compared with nights without hypoglycaemia (Table 3, Fig. 1). The same was seen in participants with reduced awareness according to the Clarke method, where EQ-5D VAS score was 7.4 (IG_{3,0} [95% CI 0.6, 14.1]) higher ($p = 0.032$) after

asymptomatic hypoglycaemic nights compared with after non-hypoglycaemic nights. No effect was observed in participants classified as having impaired awareness by the Gold method ($p = 0.34$) at threshold IG_{3,0} (data not shown). There was no effect of symptomatic nocturnal hypoglycaemia in any of the awareness classes (Table 3). Moreover, there was no association between asymptomatic nocturnal events with glucose measurements solely between 3.0 mmol/l and 3.9 mmol/l and scores on the ED-5D VAS in any of the awareness classes (normal awareness, $p = 0.29$; impaired awareness and unawareness combined, $p = 0.20$).

Influence of daytime CGM-recorded glycaemia, nocturnal hyperglycaemia and SMBG on QoL

According to the CGM data, occurrence of both asymptomatic and symptomatic episodes of daytime hyperglycaemia ($p = 0.80$) and daytime hypoglycaemia (IG_{3,9}, $p = 0.30$; IG_{3,0}, $p = 0.38$) did not influence QoL reported according to the EQ-5D VAS scale the same evening. Adjustment for these daytime glucose excursions did not alter the effect of prior nocturnal asymptomatic hypoglycaemia on QoL. Furthermore, daytime TIR was not associated with changes in EQ-5D VAS ($p = 0.12$). Occurrence of daytime

Table 3 State of hypoglycaemia awareness (according to the Hillerød Method) and QoL (assessed by the EQ-5D VAS) following overall, asymptomatic and symptomatic episodes of nocturnal hypoglycaemia at the IG_{3,9} and IG_{3,0} thresholds

Nocturnal hypoglycaemia status	Normal awareness		Impaired awareness		Unawareness	
	Mean scores (95% CI)	p^a	Mean scores (95% CI)	p^a	Mean scores (95% CI)	p^a
Overall						
IG _{3,9}		0.529		0.054		0.162
NH	83.3 (79.2, 87.4)		82.8 (78.4, 87.2)		81.8 (73.9, 89.6)	
Non-NH	82.3 (79.2, 85.5)		80.4 (76.4, 84.3)		77.1 (71.4, 82.8)	
IG _{3,0}		0.919		0.103		0.008
NH	82.6 (77.8, 87.4)		83.1 (78.3, 88.0)		87.2 (73.2, 96.1)	
Non-NH	82.4 (79.3, 85.6)		80.5 (76.5, 84.4)		76.8 (70.9, 82.7)	
Asymptomatic						
IG _{3,9}		0.444		0.073		0.150
NH	83.9 (79.1, 88.7)		82.9 (78.3, 87.5)		82.2 (74.0, 90.4)	
Non-NH	82.4 (79.2, 85.5)		80.4 (76.5, 84.4)		77.1 (71.4, 82.8)	
IG _{3,0}		0.697		0.313		0.014
NH	81.4 (75.4, 87.4)		82.5 (77.3, 87.6)		87.0 (77.7, 96.4)	
Non-NH	82.5 (79.4, 85.6)		80.6 (76.7, 84.5)		76.7 (70.8, 82.6)	
Symptomatic						
IG _{3,9}		0.941		0.714		0.922
NH	82.6 (77.4, 87.8)		81.7 (75.2, 88.2)		78.6 (60.1, 97.1)	
Non-NH	82.4 (79.3, 85.6)		80.7 (76.8, 84.7)		77.7 (72.1, 83.4)	
IG _{3,0} ^b		0.577		0.148		
NH	84.0 (77.7, 90.3)		85.1 (78.0, 92.2)		—	
Non-NH	82.4 (79.3, 85.5)		80.6 (76.7, 84.6)		—	

^a p values indicate comparison of nights without hypoglycaemia vs hypoglycaemic nights (reference: non-hypoglycaemic nights), assessed via Mixed Models analysis

^b Too few hypoglycaemic nights for analysis in 'unawareness' group

NH, hypoglycaemic night; non-NH, non-hypoglycaemic night

Fig. 1 QoL assessed by the EQ-5D VAS following nocturnal hypoglycaemia at thresholds IG_{3.9} (**a–c**) and IG_{3.0} (**d–f**) in 150 people with type 1 diabetes according to state of hypoglycaemia awareness (normal awareness, $n = 69$; impaired awareness, $n = 59$; unawareness, $n = 22$; assessed by the Hillerød method [18]). NH, hypoglycaemic nights; non-NH, non-hypoglycaemic nights. (**a**) Any episode of nocturnal hypoglycaemia (IG_{3.9}). Comparison between groups (non-NH vs NH): normal awareness, $p = 0.53$; impaired awareness, $p = 0.05$; unawareness, $p = 0.16$. (**b**) Asymptomatic nocturnal hypoglycaemia (IG_{3.9}). Non-NH vs NH: normal awareness, $p = 0.44$; impaired awareness, $p = 0.07$; unawareness, $p = 0.15$. (**c**) Symptomatic nocturnal hypoglycaemia

(IG_{3.9}). Non-NH vs NH: normal awareness, $p = 0.94$; impaired awareness, $p = 0.71$; unawareness, $p = 0.92$. (**d**) Any episode of nocturnal hypoglycaemia (IG_{3.0}). Non-NH vs NH: normal awareness, $p = 0.92$; impaired awareness, $p = 0.10$; unawareness, $p = 0.008$. (**e**) Asymptomatic nocturnal hypoglycaemia (IG_{3.0}). Non-NH vs NH: normal awareness, $p = 0.70$; impaired awareness, $p = 0.31$; unawareness, $p = 0.014$. (**f**) Symptomatic nocturnal hypoglycaemia (IG_{3.0}). Non-NH vs NH: normal awareness, $p = 0.58$; impaired awareness, $p = 0.15$. There were too few symptomatic hypoglycaemic nights at IG_{3.0} in the group with hypoglycaemia unawareness for analysis. Data are mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, NH vs non-NH

hypoglycaemia and hyperglycaemia was similar on days with and without prior nocturnal hypoglycaemia ($p = 0.59$ and $p = 0.69$, respectively). Moreover, TIR during the daytime was not related to occurrence of prior nocturnal hypoglycaemia ($p = 0.66$).

According to the EQ-5D VAS score the following day, QoL was not affected by either occurrence of nocturnal hyperglycaemia ($p = 0.53$) or occurrence of episodes with a glucose level between 4 mmol/l and 5 mmol/l ($p = 0.27$).

Lower fasting morning SMBG was associated with better QoL (EQ-5D VAS score [95% CI]: SMBG _{≤ 3.9} , 83.1 [79.6,

86.5]; SMBG_{4–10}, 82.1 [79.8, 84.5]; SMBG_{>10}, 80.1 [77.7, 82.6]; $p = 0.029$). Separate analysis of the effect of fasting morning SMBG by awareness state showed that the effect of morning SMBG on QoL was only present for participants with normal awareness (EQ-5D VAS score [95% CI]: SMBG _{≤ 3.9} , 86.2 [80.8, 91.6]; SMBG_{4–10}, 83.9 [80.5, 87.2]; SMBG_{>10}, 81.4 [78.0, 84.8]; $p = 0.042$) and not for participants with impaired awareness or unawareness, as assessed by the Hillerød method (score [95% CI]: SMBG _{≤ 3.9} , 80.8 [76.1, 85.5]; SMBG_{4–10}, 80.6 [77.2, 84.0]; SMBG_{>10}, 78.9 [75.3, 82.4]; $p = 0.31$).

Discussion

In the present study, QoL measured daily in the evening by the EQ-5D VAS was increased on days preceded by asymptomatic, but not symptomatic, nocturnal hypoglycaemia detected by blinded CGM. The QoL increment was ‘dose-dependent’ as it increased both with lower glucose nadir and longer duration of the hypoglycaemic episode, and it was transient as it was not present on the second day after the event. Furthermore, the effect was consistently confined to individuals with impaired hypoglycaemia awareness.

Overall, no clear glucose threshold for the effect of asymptomatic hypoglycaemia on QoL the following day was demonstrated. However, there was no effect of tight nocturnal glycaemic control and no significant effect of level 1 episodes with nadir between 3.0 and 3.9 mmol/l. This supports the present consensus on a glycaemic level of less than 3.0 mmol/l (level 2) for clinically important CGM-detected hypoglycaemia [23, 25].

To our knowledge, this is the first study to examine the impact of spontaneous mild nocturnal hypoglycaemia detected by blinded CGM on day-to-day changes in QoL in type 1 diabetes. The finding that asymptomatic hypoglycaemia has an impact on QoL in real life may have great importance for people with type 1 diabetes as most episodes of nocturnal hypoglycaemic are asymptomatic [11, 12]. Since blinded CGM is used in our study, the effect of asymptomatic hypoglycaemia on QoL cannot be affected by participants having recognised the episodes. This suggests a biological effect of asymptomatic hypoglycaemia on QoL, which may be very different from the negative psychological effects previously reported to be associated with symptomatic nocturnal hypoglycaemia [3, 5, 6].

Other studies based on questionnaires retrospectively examining self-reported symptomatic hypoglycaemic episodes [3, 5, 6] or experimental studies exploring the effect of insulin-induced hypoglycaemia [7, 10, 27, 28] show that hypoglycaemia is associated with poorer QoL, mood and cognitive function. In our study, there was no impact of symptomatic nocturnal hypoglycaemia on QoL or other self-reported outcomes. This may be due to differences in the used methodologies, including QoL measures and timing of the assessments in relation to the hypoglycaemic events. Thus, if the assessment had instead been performed in the morning as in other studies [7, 10, 27, 28] it may have confirmed a negative impact of symptomatic hypoglycaemia.

People with impaired awareness had the lowest overall QoL assessed by the EQ-5D VAS. As these people have many-fold higher rates of severe hypoglycaemia, this is in accordance with the reported chronic negative impact of severe hypoglycaemia on QoL [5]. The positive impact of asymptomatic nocturnal hypoglycaemia on QoL was confined to the participants with the most impaired awareness who

scored 10.3 higher on the EQ-5D VAS following nights with asymptomatic hypoglycaemia at $IG_{3,0}$, a difference well above 7, which is regarded as clinically important [21].

The concept that people with impaired awareness may react differently to hypoglycaemia compared with those with normal awareness is supported by a number of studies [29, 30] investigating the effect of experimental insulin-induced mild hypoglycaemia [29] and state of awareness [30] on brain function. The studies show that adaptive changes (or habituation) in the cerebral responses to hypoglycaemia (with attenuated symptomatic response) may occur in individuals with impaired awareness [13, 14, 31–34]. These changes may include altered fuel transport and brain metabolism with use of alternative fuels during hypoglycaemia with neuroglycopenia. Lactate is suggested as an alternative fuel when glucose levels are low in the brain, albeit only in people with impaired awareness consistent with a metabolic adaptation to recurrent hypoglycaemia in the brain [35, 36]. Further changes include deactivation of areas associated with fear, distress and perception of hypoglycaemia as an important experience (e.g. amygdala, ventral striatum, medial orbital cortex) and increased activation of areas associated with reward sensations (lateral orbitofrontal cortex) [13, 33]. Thus, hypoglycaemia (with attenuated symptomatic response) in unaware individuals seemingly does not lead to appropriate fear and discomfort as seen in aware individuals but paradoxically may have a positive rewarding effect. Clinically, this is supported by studies demonstrating that individuals with unawareness of hypoglycaemia, who often are heavily exposed to asymptomatic hypoglycaemia, may be surprisingly unconcerned about their state of unawareness [37], and a subset of individuals with type 1 diabetes has low fear of hypoglycaemia despite carrying a high risk of severe episodes of hypoglycaemia [38]. Furthermore, interventions to reduce hypoglycaemia risk can be difficult to implement due to resistance in some individuals with impaired awareness [39]. Taken together, the evidence suggests a paradoxical pleasant or rewarding effect of hypoglycaemia on the brain in people with severely impaired awareness at an unconscious level.

The finding was not explained by an effect of prior nocturnal hypoglycaemia on daytime glycaemic profiles. Neither were they explained by tight nocturnal glycaemic control, subsequent glycaemic excursions during the day or the morning fasting plasma glucose, nor by the occurrence of preceding nocturnal hyperglycaemia. However, participants with normal awareness reported better QoL with lower fasting glucose values.

We only found a positive effect of previous nocturnal hypoglycaemia on QoL assessed by the ED-5D VAS scale and not by the WHO-5 Well-Being Index. This may be explained by the fact that the ED-5D VAS scale is a questionnaire designed to assess short-term changes in QoL [20] whereas the WHO-5 Well-Being Index is developed to show changes in QoL during a 1 week time span [19]. Therefore, the

ED-5D VAS is probably more sensitive for detecting day-to-day variations resulting from previous nocturnal hypoglycaemia.

We were unable to show an effect of prior nocturnal hypoglycaemia (neither symptomatic nor asymptomatic) on mood states the following day in real life. An explanation may be that any changes in mood have recovered during the day before testing in the evening. This is supported by studies with insulin-induced mild symptomatic hypoglycaemia [10] and severe hypoglycaemia [8] in type 1 diabetes showing that recovery of mood states occurred within 30 min after restoration of euglycaemia following mild experimental hypoglycaemia [10] and within 1.5 days after an episode of severe hypoglycaemia [8].

Likewise, self-reported work efficiency was not affected by prior nocturnal hypoglycaemia. Cognitive performance is impaired during experimentally induced (both asymptomatic and symptomatic) hypoglycaemia in type 1 diabetes [28, 29] and is supposed to recover 20–75 min after restoration of euglycaemia [9, 40, 41], thus being less likely to be reflected in the evening assessment of work efficiency.

The strength of the present study is that it is based on blinded CGM data rather than SMBG. Furthermore, it is based on prospective assessment of the impact of spontaneous hypoglycaemia on QoL during daily life rather than the impact of retrospectively self-reported episodes of hypoglycaemia. A limitation to the study is the lack of data regarding sleep duration and quality. Another limitation shared with other CGM-based studies is the validity of nocturnal hypoglycaemic episodes recorded by CGM. Thus, in the early era of CGM the use of first-generation devices occasionally resulted in detection of spurious events. However, this problem is reduced with newer CGM technology including the device used in this study [42]. Moreover, the clear dose dependency of the effect of asymptomatic hypoglycaemia supports the validity of the result.

In conclusion, people with type 1 diabetes and impaired hypoglycaemia awareness transiently report improved QoL following nights with asymptomatic (but not symptomatic) hypoglycaemia. This effect, which is probably biological, increases with depth and duration of the hypoglycaemic event and lasts for only 1 day. The finding illustrates that there may exist a complex interplay between biological and psychological effects of hypoglycaemia, which may contribute to differences in perceptions of and attitudes to hypoglycaemia among people with diabetes. Understanding this day-to-day interplay is important when designing and implementing psychobehavioural interventions to prevent hypoglycaemia [43] and deserves further scientific attention.

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Authors' relationships and activities HUA owns stocks in Novo Nordisk, has served on advisory boards for Novo Nordisk, Abbott and Astra Zeneca, and has received lecture fees from Nordic Infucare. UPB has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Novo Nordisk and Zealand Pharma and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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