Associations Between Hypoglycemia Awareness Status and Symptoms of Hypoglycemia Among Adults with Type 1 or Insulin-Treated Type 2 Diabetes Using the Hypo-METRICS Smartphone Application

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A comparison of the rates of clock-based nocturnal hypoglycemia and hypoglycemia whilst asleep among people living with diabetes: findings from the Hypo-METRICS study

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Running title: Comparing clock-based nocturnal hypoglycemia and hypoglycemia whilst asleep among adults with diabetes

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Abstract

Introduction

Nocturnal hypoglycemia is generally calculated between 00:00 and 06:00. However, those hours may not accurately reflect sleeping patterns and it is unknown whether this leads to bias. We therefore compared hypoglycemia rates whilst asleep to those of clock-based nocturnal hypoglycemia in adults with type 1 (T1D) or insulin-treated type 2 diabetes (T2D).

Methods

Participants from the Hypo-METRICS study wore a blinded continuous glucose monitor and a Fitbit Charge 4 activity monitor for 10 weeks. They recorded details of episodes of hypoglycemia using a smartphone app. Sensor-detected hypoglycemia (SDH) and person-reported hypoglycemia (PRH) were categorized as nocturnal (00:00-06:00hrs) vs diurnal and whilst asleep vs awake defined by Fitbit sleeping intervals. Paired sample Wilcoxon tests were used to examine the differences in hypoglycemia rates.

Results

574 participants (47% T1D, 45% women, 89% White, median (IQR) age 56 (45-66) years and HbA_{1c} 7.3% (6.8-8.0)) were included. Median sleep duration was 6.1h (5.2-6.8), bedtime and waking time approximately 23:30 and 07:30 respectively. There were higher median weekly rates of SDH and PRH whilst asleep than clock-based nocturnal SDH and PRH among people with T1D, especially for SDH<70 mg/dL (1.7 vs 1.4, $p<0.001$). Higher weekly rates of SDH whilst asleep than nocturnal SDH were found among people with T2D, especially for SDH<70 mg/dL (0.8 vs 0.7, $p<0.001$).

Conclusion

Using 00:00 to 06:00 as a proxy for sleeping hours may underestimate hypoglycemia whilst asleep. Future hypoglycemia research should consider the use of sleep trackers to record sleep and reflect hypoglycemia whilst asleep more accurately.

Introduction

Hypoglycemia is a common adverse effect of insulin treatment in people with diabetes (1). During sleep, physiological responses to hypoglycemia and mental arousal are reduced, leading to a lower likelihood that individuals will wake up and take corrective action (2–4). As a result, hypoglycemic episodes occurring at night tend to last longer and be more severe than those occurring during waking hours (4). In addition, nocturnal hypoglycemia has been associated with lower quality of life, higher fatigue levels and reduced productivity (5). Qualitative evidence has also shown that people with diabetes report fear and anxiety about going to sleep at night, often linked with greater worries about hypoglycemia and fear of dying as a result of hypoglycemia (6,7).

Key research studies to date that have reported on nocturnal hypoglycemia rates (8–10) used a clock-based method to distinguish between daytime and nighttime, based on the assumption that sleep occurs between pre-defined hours (e.g. 00:00-06:00 or 23:00-07:00). This approach is pragmatic and designed to provide consistency between studies, but it may have contributed to biased results. This bias is due to the fact that there is intra- and inter-individual variability in sleeping patterns in the general population and in people with diabetes, often as a result of biological (e.g., individual's chronotype) and environmental (e.g., employment status or social obligations) factors (11,12). In addition, given the reduced physiological and behavioral responses to hypoglycemia both relate to sleep status rather than time of day, the ideal would be to measure sleep adequately when estimating the rates of nocturnal hypoglycemia.

Smartphone technologies and wearable devices that capture and monitor daily life sleep and wake cycles in real-time are increasingly available, accessible, and user-friendly (13). New generation devices generally estimate sleep start and end times and sleep stages using sensors which detect body movement, heart rate and heart rate variability (14). Recent validation studies of wearable devices such as the Fitbit (Fitbit, Inc.; San Francisco, California, United States) have shown promising results when compared to the gold standard polysomnography method in accurately measuring sleep in clinical (15,16) and non-clinical populations (17). Whilst some hypoglycemia studies have used activity monitors to record sleep periods previously (18,19), no studies to date have assessed whether the rates of conventionally calculated clock-based nocturnal hypoglycemia accurately reflect those of hypoglycemia whilst asleep. This study therefore aimed to address this gap by comparing the rates of clock-based nocturnal hypoglycemia to those of hypoglycemia whilst asleep, as measured using a real-time sleep tracker device.

Methods

1. Study population

Hypoglycaemia—MEasurement, ThResholds and ImpaCtS (Hypo-METRICS) is a 10-week observational study which was conducted across nine UK and EU sites between October 2020 and August 2022, as part of the Hypo-RESOLVE project (20). Full details of the study methods have been reported previously (21). Participants recruited to the study were 602 adults aged between 18 and 85 years old with type 1 diabetes or insulin-treated type 2 diabetes who had at least one episode of hypoglycemia in the three months prior to the study. People who worked regular night shifts were excluded from the study.

Participants wore a blinded modified continuous glucose monitor (CGM) device (Abbott Freestyle Libre 2™) and a sleep and activity tracking device (Fitbit Charge 4™) continuously

for 10 weeks. Participants were asked to record all episodes of hypoglycemia using daily questionnaires and a real-time symptom tracker in the novel Hypo-METRICS smartphone application. Full details of the design of the Hypo-METRICS app have been published previously (22).

Ethical approval for the study was granted by Oxford B Research Ethics Committee (UK), CMO Region Arnhem- Nijmegen (Netherlands), Ethikkommission der Medizinischen Universität Graz (Austria), Videnskabsetisk Komite for Region Hovedstaden (Denmark) and Comite De Protection Des Personnes SUD Mediterrannee IV (France). All participants provided informed written consent for the study.

2. Study sample

Hypo-METRICS participants were included in the present study if Fitbit sleep, CGM and Hypo-METRICS app data were all adequately collected during the study. Participants with no Fitbit and/or CGM data (due to technical issues) were excluded. Participants for whom all hypoglycemic events recorded had missing sleep data at the time of the event were also excluded.

3. Hypoglycemia classification

Two types of hypoglycemic events were considered: sensor-detected hypoglycemia (SDH) recorded with the CGM, and person-reported hypoglycemia (PRH) recorded with the Hypo-METRICS app. SDH was defined as glucose readings below a threshold (70 mg/dL and 54 mg/dL) for a minimum of 15 minutes, in accordance with consensus guidelines (23). PRH was defined as a symptomatic event that resolved on carbohydrate ingestion or a self-measured glucose below 4 mmol/L, reported by participants using the Hypo-METRICS app.

4. Night and sleep classification

Nighttime was defined using the hours between 00:00 and 06:00. Sleep time was determined using start time and end time of sleep as generated by the Fitbit Charge 4™ which uses movement patterns and heart rate variability to determine whether a person is asleep (17).

5. Weekly rates of clock-based nocturnal hypoglycemia and hypoglycemia whilst asleep

Each hypoglycemic event was categorized based on their clock-based nocturnal status and Fitbit-detected sleep status. A SDH was classified as 'nocturnal' if it occurred between 00:00 and 06:00 and 'diurnal' if it occurred between 06:01 to 23:59. A SDH was classified as 'whilst asleep' if it occurred between start time and end time of sleep (including daytime sleep) as identified by the Fitbit and 'whilst awake' if it occurred outside sleep intervals. If a SDH interval overlapped between nocturnal/diurnal and/or asleep/awake periods, it was attributed the nocturnal/sleep status for which the area under the curve was the greatest. Each PRH was categorized using the same method as for SDH.

For each participant and hypoglycemic event type (SDH <70 mg/dL, SDH <54 mg/dL and PRH), we calculated two weekly rates: the rates of clock-based nocturnal hypoglycemia and the rates of hypoglycemia whilst asleep, as the number of events divided by the number of study weeks.

6. Statistical analysis

A descriptive analysis was conducted to describe participants' baseline characteristics. Sleep characteristics as derived from the Fitbit were also described. Categorical variables were presented as frequencies and percentages. Continuous variables were checked for normality using the Shapiro-Wilk test and skewed data were presented as median and interquartile range (IQR). Sleeping patterns were visually assessed firstly using individual data from two participants as illustrative examples and secondly, histograms of the distributions of bedtimes (centered around 00:00) and wake up times (centered around 06:00) in the overall sample.

Paired-sample Wilcoxon tests were used to estimate the differences in the weekly rates between hypoglycemia whilst asleep and clock-based nocturnal hypoglycemia. This was conducted for SDH <70 mg/dL, SDH <54 mg/dL and PRH, separately for participants with type 1 diabetes and type 2 diabetes.

All analyses were conducted in R (R V.4.2.2 & R Studio V. 2023.06.2 for Windows).

Results

602 participants were recruited for the Hypo-METRICS study; 589 had sleep data, CGM values and Hypo-METRICS app data and of those, 575 were eligible for inclusion in the present study (Figure 1).

1. Participants' characteristics

The study sample included participants who were predominantly White with an almost equal representation of both women and men. Diabetes duration was moderate and glucose control relatively good. One fifth of the sample had impaired awareness of hypoglycemia. Participants with type 1 diabetes predominantly used continuous glucose monitoring (CGM) as their usual method of glucose monitoring whilst participants with type 2 diabetes mostly self-monitored their blood glucose (Table 1). Median percentage of time the blinded CGM was active was 95.3% (89.2-98.2) and Hypo-METRICS app questionnaire completion rates 91.1% (84.4-95.7). Almost all participants experienced at least one episode of SDH <70 mg/dL (96.3%), SDH <54 mg/dL (83.9%) or PRH (97.2%) during the study.

2. Sleep characteristics and patterns

Median (IQR) number of nights with sleep data available per participant was 69 (65-70). Participants with type 1 diabetes had a median time asleep of 6.4 hours (5.8-7.0) and participants with type 2 diabetes had a median time asleep of 5.6 hours (4.6-6.5).

In the overall sample, 61.7% of the bedtimes recorded by the Fitbit were between 12:00 and 23:59 and 78.6% of waking up times were between 06:01 and 18:00. Only about 5% of the sleeping periods recorded by the Fitbit during the study fell within the 00:00-06:00 time window. Figure 2 highlights intra- and inter-individual variability in sleeping patterns in two participants over the course of the study. Figure 3 shows that in participants with type 1 diabetes, the median bedtime (IQR) (23:28 (22:34; 00:33)) was before 00:00 and wakeup time (07:31 (06:31; 08:35)) after 06:00. Similarly, in participants with type 2 diabetes, median bedtime was 23:27 (22:08; 01:05) and wake up time was 07:24 (05:58; 08:49).

3. Clock-based nocturnal hypoglycemia and hypoglycemia whilst asleep

Overall, 25,813 SDH <70 mg/dL (30.1% nocturnal and 34.7% whilst asleep), 6,022 SDH <54 mg/dL (39.8% nocturnal and 46.1% whilst asleep) and 16,254 PRH (20.7% nocturnal and 23.1% whilst asleep) were recorded. The analysis of the overlap between hypoglycemia whilst asleep and clock-based nocturnal hypoglycemia events showed that for all hypoglycemia types (SDH <70 mg/dL, SDH <54 mg/dL and PRH), approximately 25-30% of hypoglycemia events whilst asleep were not identified as clock-based nocturnal hypoglycemia.

Among participants with type 1 diabetes, weekly hypoglycemia rates whilst asleep were higher than those of clock-based nocturnal hypoglycemia for SDH <70 mg/dL, SDH <54 mg/dL and PRH (all with $p<0.001$, Figure 4A). Among participants with type 2 diabetes, weekly hypoglycemia rates whilst asleep were higher than those of clock-based nocturnal hypoglycemia for SDH <70 mg/dL ($p<0.001$) and SDH <54 mg/dL ($p<0.001$), but not PRH (Figure 4B).

Discussion

This study is the first to date to compare the rates of hypoglycemia whilst asleep using a sleep-tracking wearable device to those of clock-based nocturnal hypoglycemia. Firstly, we have shown in both type 1 and type 2 diabetes that median sleep duration was close to 6 hours during the study as recorded by the Fitbit. Secondly, we found that the period from 00:00 to 06:00, that is typically used to define the night in counting hypoglycemic episodes, did not accurately reflect participants' sleeping patterns. Lastly, the rates of hypoglycemia whilst asleep were higher than those of clock-based nocturnal hypoglycemia, for SDH <70

mg/dL, SDH <54 mg/dL and PRH in type 1 diabetes and for SDH <70 mg/dL and <54 mg/dL in type 2 diabetes.

It was shown that participants in the present study slept for approximately 6 hours which is consistent with previous studies reporting sleep durations of 5.97 hours (24), 6.2 hours (25), 6.3 hours (26) and 6.7 hours (27) measured using accelerometers or wireless sleep monitors in people with diabetes. Nevertheless, the hours between 00:00 and 06:00 did not align with their chronotypes as median bedtime was close to 23:30 and waking up time close to 7:30 in both type 1 and type 2 diabetes. Comparable sleeping times have been described before in type 1 diabetes (bedtime: 23:44 and wake up time: 07:28) (28) and type 2 diabetes (bedtime: 23:30) (27), among people categorized as having an 'intermediate' chronotype i.e., a person with neither a preference for morning or evening in their sleep and awake cycles (29). Beyond participants' chronotypes, it is also possible that professional, personal and social obligations which are part of daily life (11,12) contributed to the fact that 00:00 to 06:00 did not align with daily life sleeping patterns in our study. In addition, recruitment for the Hypo-METRICS study was partly conducted during the COVID-19 pandemic, and whilst a recent study showed that COVID restrictions were not associated with differences in sleep duration in people with type 2 diabetes in the United Kingdom (30), it is likely that different restrictions over the five countries involved in the present study may have impacted daily lives, including sleeping patterns and timings. This study has also demonstrated that using a clock-based method to examine nocturnal hypoglycemia underestimates the rates of hypoglycemia whilst asleep and this may partly be because 00:00 to 06:00 did not align with participants' sleeping patterns, as previously discussed. This partly corroborates data from the Diabetes Control and Complications Trial which showed that 55% of severe hypoglycemic events started during sleep (episodes of hypoglycemia and their characteristics such as sleep

status were prospectively recorded by participants) but only 43% occurred between 00:00 and 08:00 hours (31). The rates of nocturnal hypoglycemia occurring between 00:00 and 06:00 observed in the present study were higher than previously reported (8,9,32) but still up to 30% lower than those of hypoglycemia whilst asleep, whether sensor-detected or person-reported. This is essential as underestimating the rates of hypoglycemia whilst asleep may mean that we are currently underestimating its impact on factors such as work productivity and general wellbeing and quality of life for people with diabetes. It would thus be important for future research to establish whether the impact of clock-based nocturnal hypoglycemia differs from this of hypoglycemia whilst asleep.

Taken together, our findings stress the importance of using real-time wearable sleep trackers when the incidence of hypoglycemia, and particularly hypoglycemia during sleep is an important research outcome. It is acknowledged that this may not always be feasible but other methods such as smartphone-based sleep trackers and self-reported sleeping times in diaries could be used, although they may be less accurate than wearable trackers (33–35). Nevertheless, these methods have the advantage of recording actual sleeping patterns and timings rather than arbitrarily choosing sleeping times as per the clock-based method which, as shown in the present study, makes a significant difference to the estimated hypoglycemia rates whilst asleep.

The main strength of this study is the use of a validated device to objectively record sleep to examine sleeping patterns and estimate the rates of hypoglycemia whilst asleep, which has never been conducted before in a substantial sample of people with diabetes (n=575) and for an extensive study duration (n=10 weeks). Additionally, our results are based on robust data as participants' data completion rates were relatively high for the CGM, Fitbit and Hypo-

METRICS app. Our study was limited by Fitbit Charge devices tendency to overestimate time asleep as suggested by previous validation studies (16,17). Beyond differences in the way sleep/night-time was defined, it is also possible that factors such as chronotype, short periods of time awake during the night, percentage of time in each sleep stage which have not been accounted for in this study, could have contributed to our results. Future research could therefore investigate to which extent those factors contribute to differences between hypoglycemia whilst asleep and clock-based nocturnal hypoglycemia. We cannot rule out a potential selection bias as recruited participants reported at least one episode of hypoglycemia in the months prior to the study which may have inflated hypoglycemia rates in comparison to previous large population-based studies. Nevertheless, the demography of our recruited participants was not otherwise dissimilar from other populations, in terms of age, diabetes duration, or prevalence of impaired hypoglycemia awareness. Lastly, the predominant ethnic group was White in the present study which may limit the generalizability of the findings.

To conclude, the conventional clock-based method to examine nocturnal hypoglycemia underestimates the rates of hypoglycemia whilst asleep by up to 30%. Our findings will need to be reproduced but nevertheless suggest that using real-time sleep trackers to record sleep when examining hypoglycemia whilst asleep may allow researchers and clinicians to (1) better reflect its rates and (2) better account for underpinning biological and environmental factors that can affect sleep duration and timings. Thus, with the explosion of sleep-tracking technologies available, future hypoglycemia research should consider using validated real-time sleep trackers as a standard to report on the rates of hypoglycemia whilst asleep. When the use of real-time sleep trackers is not feasible, our novel data could allow researchers to estimate the possible error in nocturnal hypoglycemia rates.

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Conflict of interests

GME's position at King's College London is funded by a research grant from Novo Nordisk as part of their contribution to the Hypo-RESOLVE consortium.

SAA has served on advisory boards for NovoNordisk and Medtronic and has spoken at an educational symposium sponsored by Sanofi.

MLE has served on advisory boards and/or received lecture fees and/or research support from NovoNordisk, Eli Lilly, AstraZeneca, Medtronic, Dexcom, Ypsomed, Abbott Diabetes Care, Roche, NGM Pharma, Zucara, Pila Pharma.

UPB has served on advisory boards and has received lecture fees from Sanofi and Novo Nordisk.

JKM is a member of RM and has served on advisory boards of Abbott Diabetes Care, Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Embecta, Medtronic, NovoNordisk A/S, Roche Diabetes Care, Sanofi-Aventis, Viatris and has received speaker honoraria lecture fees from A. Menarini Diagnostics, Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtrust, MSD, NovoNordisk A/S, Roche Diabetes Care, Sanofi, Servier,Sanofi and Ypsomed. She is shareholder of decide Clinical Software GmbH and elyte Diagnostics where she also serves as CMO.Novo Nordisk.

BDG has received research support from Novo Nordisk.

ER has served as consultant/advisor for Abbott, Air Liquide SI, Astra-Zeneca, Boehringer-Ingelheim, Dexcom, Eli-Lilly, Hillo, Insulet, Medirio, Novo-Nordisk, Roche, Sanofi-Aventis, Tandem, and received research support from Dexcom and Tandem.

JS has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes [ACBRD]) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes. JS has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes, and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes.

PC has received personal fees Abbott Diabetes Care, Insulet, Dexcom, Novo Nordisk, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes. Research funding support from Abbott Diabetes Care, Medtronic and Novo Nordisk.

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Table

Table 1. Participants' baseline characteristics

Characteristic	Overall N=575	Type 1 N=271	Type 2 N=304
Age (years), median (IQR)	56 (45-66)	47 (30-56.5)	63 (55-69)
HbA_{1c} (%), median (IQR)	7.3 (6.8-8)	7.3 (6.7-7.8)	7.4 (6.8-8.3)
Diabetes duration (years), median (IQR)	19 (11-27)	19 (9-33)	19 (13-25)
Impaired awareness of hypoglycemia, n (%)	138 (24)	58 (21.4)	80 (26.3)
Sex, n (%)			
Women	260 (45.2)	147 (54.2)	113 (37.2)
Men	313 (54.4)	122 (45)	191 (62.8)
Other	2 (0.3)	2 (0.7)	0
Ethnicity, n (%)			
Asian	16 (2.8)	3 (1.1)	13 (4.3)
Black	14 (2.4)	4 (1.5)	10 (3.3)
White	512 (89)	238 (87.8)	274 (90.1)

Figure legends

Figure 1. Flowchart of study participation

Figure 2. Sleeping patterns during the study in (A) a participant with type 1 diabetes and (B) a participant with type 2 diabetes

Figure 3. Histograms of the distribution of bedtimes and waking up times in (A) Type 1 diabetes and (2) Type 2 diabetes

Figure 4. Weekly rates of clock-based nocturnal hypoglycemia and hypoglycemia whilst asleep in (A) Type 1 diabetes and (B) Type 2 diabetes