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Time spent in hypoglycemia according to age and time-of-day: Observations during closed-loop insulin delivery

Short title: Hypoglycemia in closed-loop studies

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Abstract:

Objective: We aimed to assess whether percentage of time spent in hypoglycemia during closed-loop insulin delivery differs by age-group and time-of-day.

Methods: We retrospectively analyzed data from hybrid closed-loop studies involving young children (2-7 years), children and adolescents (8-18 years), adults (19-59 years), and older adults (≥60 years) with type 1 diabetes. Main outcome was time spent in hypoglycemia <3.9mmol/l (<70 mg/dl). Eight weeks of data for 88 participants were analyzed.

Results: Median time spent in hypoglycemia over the 24-hour period was highest in children and adolescents (4.4%; [IQR 2.4-5.0]) and very young children (4.0% [3.4-5.2]), followed by adults (2.7% [1.7-4.0]), and older adults (1.8% [1.2-2.2]); p<0.001 for difference between age-groups. Time spent in hypoglycemia during nighttime (midnight-05:59) was lower than during daytime (06:00-23:59) across all age-groups. **Conclusion:** Time in hypoglycemia was highest in the pediatric age-group during closed-loop insulin delivery. Hypoglycemia burden was lowest overnight across all age-groups.

Introduction

Hypoglycemia remains an important limiting factor in achieving optimal glycemic control in persons with type 1 diabetes.[1] Closed-loop insulin delivery systems, which consist of an insulin pump, a continuous glucose monitor (CGM), and an algorithm that directs insulin delivery in response to real-time glucose levels, have been shown to improve glycemic control whilst not leading to an increased time spent in hypoglycemia.[2]

However, despite use of closed-loop systems, hypoglycemia continues to pose a challenge in the management of type 1 diabetes.[2] To the best of our knowledge, no study has directly compared the percentage of time spent in hypoglycemia across different age-groups and by time-of-day in closed-loop insulin therapy. In the present analysis, we assess whether percentage of time spent in hypoglycemia during closed-loop insulin delivery differs by age-group and time-of-day.

Research Design and Methods

We retrospectively analyzed 8 weeks of data from four multicenter, multinational studies (Austria, Switzerland, Germany, Luxembourg, UK, US) using hybrid closed-loop insulin delivery in persons with type 1 diabetes (trial registrations NCT04055480, NCT04025762, NCT02925299, and NCT03784027).[3-6] Participants were divided into four age-groups: young children (2-7 years), children and adolescents (8-18 years), adults (19-59 years), and older adults (≥60 years).

Inclusion criteria included type 1 diabetes diagnosis (World Health Organization criteria) for more than 6 months (young children and adults)[4, 5] or 12 months (adolescents and older adults)[3, 6] and insulin pump therapy for minimum 3 months. Inclusion criteria for glycated hemoglobin (HbA1c) at screening varied between studies: upper limit was 10% (86 mmol/mmol) in adolescents, adults and older adults[3, 4, 6] and 11% (97 mmol/mol) in young children [5]. There was no lower threshold for HbA1c in all but one study (lower limit set at 7.0% (53 mmol/l) for children and adolescents)[6].

Participants and/or parents/caregivers gave written informed consent. All studies received national regulatory and independent ethical approval.

Closed-loop insulin delivery

The hybrid closed-loop system comprised the CamAPS FX app (CamDiab, Cambridge, UK) residing on an unlocked Android smartphone, a CGM device (Dexcom G6; Dexcom, San Diego, CA, USA), and an insulin pump (Dana Diabecare RS; Sooil, Seoul, South Korea). Every 8 to 12 minutes, the adaptive model predictive control algorithm residing on the CamAPS FX app automatically calculated the insulin infusion rate which was then communicated wirelessly to the study pump.[4] The closed-loop algorithm has a default target glucose level of 5.8 mmol/l (104 mg/dl), which is adjustable between 4.4 and 11.0 mmol/L (79 and 198 mg/dl) across different times of day and night.[3]

Data analysis and statistical methods

The main outcome was time spent in hypoglycemia (sensor glucose < 3.9 mmol/l / 70 mg/dl) by time-of-day. Daytime was defined as 06:00 to 23:59 and nighttime was defined as midnight to 05:59. To ensure equal representation across all age groups, 22 participants were included from each study. For three out of the four studies, the 22 participants were randomly selected using random sampling. For one study (among children and adolescents) only data from 22 participants using the CamAPS FX configuration were available as the other participants in the study used the FlorenceM configuration. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge, Cambridge, UK), and statistical analyses were performed using R (version 4.4.1, R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean±standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data. To compare the difference between age-groups for time spent in hypoglycemia, data were winsorized at the 10th and 90th percentile and one-way ANOVA with post hoc analysis using the Tukey test was performed. The reported P values are not adjusted for multiple testing. P values <0.05 were considered statistically significant.

Results

Eight weeks of data for 88 participants were analyzed. Table 1 shows the demographic characteristics of the study population. Mean age was 5.5±1.5, 12.5±2.1, 38.3±9.2, and

66.8±5.5 years for very young children, children and adolescents, adults, and older adults, respectively. Around 41% of very young children were females, and 54% of children and adolescents, adults, and older adults were females. Duration of diabetes ranged from 1.1±1.0 among very young children to 38.3±12.0 among older adults. Mean HbA1c at baseline was 7.3±0.7% (56.1±8.1 mmol/mol), 8.0±0.9% (64.0±9.9 mmol/mol), 7.3±0.8% (56.7±8.5 mmol/mol), and 7.7±0.8% (60.3±8.6 mmol/mol) for very young children, children and adolescents, adults, and older adults, respectively.

Glycemic outcomes per study are presented in Table 2. The median percentage of time when sensor glucose was below target glucose range (<3.9 mmol/l / 70 mg/dl) over the 24-hour period was highest for children and adolescents at 4.4% (IQR 2.4-5.0), followed by very young children at 4.0% (IQR 3.4-5.2), then adults (2.7%; IQR 1.7-4.0), and lowest for older adults (1.8%; IQR 1.2-2.2). The mean percentage of time when sensor glucose was in target glucose range (3.9 to 10.0 mmol/L / 70 to 180 mg/dl) was highest among older adults (78.4±8.2%) and lowest among children and adolescents (67.8±6.2%).

The distribution of the median time in hypoglycemia over the 24-hour period across the four age-groups is shown in Figure 1. Percentage time spent in hypoglycemia appeared to be greatest between 12:00 to 14:00 and 18:00 to 20:00 among very young children and between 12:00 to 14:00 and 18:00 to 21:00 among children and adolescents. Among adults and older adults, time spent in hypoglycemia was more evenly distributed throughout the 24-hour period but had a tendency to be higher between 12:00 to 14:00 and 18:00 to 20:00.

Median percentage time spent in hypoglycemia by age-group and time-of-day (daytime versus nighttime) is shown in Figure 2. During daytime, median time spent in hypoglycemia was highest in children and adolescents (5.1%; IQR 2.8-5.8), followed by very young children (4.6%: IQR: 3.8-5.9), adults (3.1%; IQR: 1.7-4.4), and finally older adults (2.1%; IQR: 1.4-2.5); p<0.001 for the difference between age-groups. Similarly, during nighttime, median time spent in hypoglycemia was highest in very young children at 2.6% (IQR: 1.3-3.7) while older adults spent the least amount of time in hypoglycemia at 1.0% (IQR: 0.6-1.3); p<0.001 for the difference between age-groups.

Discussion

In this retrospective analysis of data from four hybrid closed-loop studies across all age-groups from very young children to older adults, we found that hypoglycemia burden is highest in the pediatric age-groups and lowest in older adults during both the daytime and nighttime.

International guidelines recommend that persons with T1D should spend more than 70% of time within target glucose range 3.9-10.0 mmol/L (70-180 mg/dl) and less than 4% of time (or less than 1% of time for older adults) below target glucose range <3.9 mmol/L (70 mg/dl).[7, 8] Studies have shown that the use of hybrid closed-loop can improve glycemic outcomes as compared to usual care across all age-groups.[9-14] We found that adults were able to achieve these glycemic targets during both daytime and nighttime. Older adults were within target for time below range during nighttime, and slightly above target during daytime. The pediatric age-groups, however, spent a slightly longer time in hypoglycemia over the 24-hour period than recommended in the guidelines. This finding is in line with previous studies that have shown that children experience hypoglycemia more frequently than older persons with type 1 diabetes[15] Factors that can increase the risk of hypoglycemic events in the pediatric age-groups include increased physical activity as compared to their older counterparts and skipped meals.[15, 16]

We found that the pediatric age-group spent more time in hypoglycemia between 12:00 to 14:00 and 18:00 to 20:00. Although information on participants' mealtimes is not available in the current analysis, the timing of these events suggests postprandial hypoglycemia. We found a similar, yet less pronounced, pattern for time spent in hypoglycemia for adults and older adults. This finding reinforces the importance of accurate carbohydrate counting, the timely administration of bolus insulin before meals, use of extended boluses for meals high in protein/fat, as well as the use of ultra-fast-acting insulin as measures to reduce the burden of hypoglycemia in persons with type 1 diabetes.[17, 18] However, some causes of hypoglycemia are difficult to prevent and/or manage (e.g., skipped meals), which highlights the challenges involved in managing type 1 diabetes in these age-groups despite use of closed-loop insulin systems.

Time spent in hypoglycemia was higher during the daytime than nighttime across all age-groups, in line with previous studies.[10, 11, 19] Differences in time spent in hypoglycemia across age-groups were more pronounced during the daytime than the nighttime. This is unsurprising as most of the insulin delivered overnight is closed-loop driven insulin, rather than user-driven bolus insulin[11] with safety measures to reduce the risk of hypoglycemia. Moreover, other factors that can influence glucose levels during the daytime (e.g., meals, exercise) are generally absent at night[11].

To our knowledge, this is the first study that aimed to compare the effect of closed-loop therapy on time spent in hypoglycemia by age-group and time-of-day. Strengths of this study are therefore the inclusion of several age-groups across the lifespan in the analyses, and the multinational unrestricted-living study design. The limitations of the current study include the retrospective analysis, the relatively short follow-up period as well as the minor differences in study design. Although the participants included in the present analysis were randomly selected for three out of the four studies, we cannot rule out selection bias among the 8-18 years age-group as only data for 22 participants who used the CamAPS FX configuration were available. Moreover, participants in the ≥60 years age-group might not be completely representative of the general population of older adults with type 1 diabetes due to the requirement for insulin pump therapy (although this was a requirement for participants in all included studies). While older adults received the same training as participants in the other age-groups, data on whether higher personal glucose targets were more widely applied in older adults were not recorded. A final limitation is that C-peptide was not measured in all studies and therefore not included in the present analysis.

Conclusions

In conclusion, in persons with type 1 diabetes using closed-loop therapy, hypoglycemia burden was low overall across all age-groups but was higher in the pediatric age-groups as compared to adults. Time in hypoglycemia was lowest during the nighttime. Our results highlight the challenges involved in managing type 1 diabetes in the pediatric age-groups, despite use of closed-loop insulin therapy. Strategies designed to reduce potentially

avoidable causes of hypoglycemia such as accurate carbohydrate counting, and timely administration of prandial boluses, can be reinforced.

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Conflict of Interest:

RH reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from BBraun; patents related to closed-loop, and being director at CamDiab. JW reports receiving speaker honoraria from Ypsomed. HA is a consultant at CamDiab. MEW is a consultant at CamDiab and reports patents related to closed-loop. CKB reports receiving consultancy fees from CamDiab and speaker honoraria from Ypsomed. SH reports speaker & advisory board fees from Dexcom, Medtronic, Sanofi & Ypsomed; being director at ASK Diabetes Ltd and receiving consulting / training fees from CamDiab. LB reports receiving research support from Dexcom and CamDiab. REJB reports receiving speaking honoraria from Eli Lilly and Springer Healthcare, and sitting as a voluntary unpaid member of the NovoNordisk UK Foundation Research Selection committee. FMC reports receiving speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk and Insulet, and consultancy fees from Abbott Diabetes Care. EFR reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory boards for Eli Lilly and

Sanofi. MLE is a clinical triallist with or has served on advisory boards or received speakers or writers fees from Medtronic, Dexcom, Abbott Diabetes Care, Roche, AstraZeneca, Novo Nordisk, Eli Lilly, Zucara, Pila Pharma, and Imcyse Pharma. SEH has received speaker honoraria by Eli Lilly, Vertex, Minimed Medtronic, Insulet, Ypsomed, Dexcom and Sanofi. TMK reports having received speaker honoraria from Eli Lilly and Novo. LL has received personal fees from Abbott Diabetes Care, Dexcom, Insulet, Medtronic, Novo Nordisk, Sanofi, and Diabetes Care. JKM is a member on the advisory board of Becton-Dickinson, Eli Lilly, embecta, Medtronic, NovoNordisk, Pharmasens AG, Roche Diabetes Care, and Sanofi-Aventis and received speaker honoraria from Abbott Diabetes Care, A. Menarini Diagnostics, Becton-Dickinson, Dexcom, Eli Lilly, Medtrust AG, NovoNordisk, Roche Diabetes Care, Sanofi-Aventis, Servier and Ypsomed. HT reports receiving research support from Dexcom and speaker honoraria from Eli Lilly. BRM has received speaker honoraria from Abbott Diabetes Care, Eli Lilly, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi and Menarini and has been on the advisory boards of Eli Lilly, Roche Diabetes Care and Abbott Diabetes Care. CdB has received speaker honoraria from Minimed Medtronic, and has been member of their European Psychology and e learning Advisory Board. JMA reports training fees from CamDiab. MT reports heaving received speaker honoraria from Eli Lilly, Novo Nordisk and Medtronic and advisory board fees from Abbott Diabetes Care. MN has received travel grant support from Sanofi, Janssen and Eli Lilly and was previously chair of the Young Diabetologists' and Endocrinologists' Forum in the UK, which uses unrestricted sponsorship from industry partners to deliver educational programs for health care professionals. LD has received advisory board payment from Dexcom and a fee for chairing an educational session for Novo Nordisk. PN, RL, AG, ND, and AT have no disclosures.

Author Contributions and Guarantor Statement:

HA, CKB, MN, MEW, JW and RH co-designed the analysis. HA, RL, MEW, JW and RH carried out or supported data analysis, including statistical analysis. HA wrote the manuscript. MEW, JMA, CKB, LB, CdB, REJB, FMC, EFR, AG, SEH, TMK, LL, BRM, HT, AT, PN and RH co-designed the clinical studies. RH designed the control algorithm. JW, JMA, CKB, SH, LB, CdB, REJB, FMC, MLE, EFR, AG, SEH, TMK, LL, JKM, PN, BRM, HT, AT, LD and ND screened

and enrolled participants, provided patient care and/or took study samples. All authors critically reviewed the manuscript. HA and RH are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation:

Data from this manuscript was presented as an abstract for poster presentation at the 16th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD 2023).

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Table 1. Characteristics of the participants at baseline by age-group.

Characteristic	2-7 years	8-18 years	19-59 years	≥60 years
N	22	22	22	22
Age (years)				
Mean	5.5±1.5	12.5±2.1	38.3±9.2	66.8±5.5
Range	2-7	9-16	24-53	60-80
Sex - no. (%)				
Female	9 (41)	12 (54)	12 (54)	12 (54)
Male	13 (59)	10 (46)	10 (46)	10 (46)
Race - no. (%)				
White	18 (81)	19 (86)	21 (95)	22 (100)
Black	1 (5)	0	0	0
Hispanic or Latino	0	0	0	0
Asian	0	2 (9)	0	0
Other	2 (9)	0	1 (5)	0
More than one race	1 (5)	1 (5)	0	0
Unknown	0	0	0	0
Duration of diabetes (years)				
Mean	1.1±1.0	6.0±2.2	23.8±11.2	38.3±12.0
Range	0-2	3-11	5-46	13-61
Glycated hemoglobin at screening				
Percent	7.3±0.7	8.0±0.9	7.3±0.8	7.7±0.8
Millimoles per mole	56.1±8.1	64.0±9.9	56.7±8.5	60.3±8.6
BMI	66.1±20.1*	57.0±20.5*	27.1±4.8	28.0±5.0

Data are n (%) or mean (SD). BMI = body mass index

*BMI percentile

Table 2. Glycemic and insulin outcomes per age-group.

End point	2-7 years N=22	8-18 years N=22	19-59 years N=22	≥60 years N=22
Time spent at glucose level <3.9 mmol/l (70 mg/dl) (%)	4.0 (3.4-5.2)	4.4 (2.4-5.0)	2.7 (1.7-4.0)	1.8 (1.2-2.2)
Time spent at glucose level <3.0 mmol/l (54 mg/dl) (%)	0.8 (0.6-0.9)	0.8 (0.5-1.2)	0.6 (0.2-0.8)	0.2 (0.1-0.3)
Time spent at glucose level 3.9-10.0 mmol/l (70-180 mg/dl) (%)	72.5±6.5	67.8±6.2	75.2±8.5	78.4±8.2
Time spent at glucose level >10.0 mmol (180 mg/dl) (%)	23.1±6.8	28.3±6.6	21.7±9.1	19.8±8.7
Total daily insulin (U/kg/day)	0.8±0.2	1.1±0.2	0.6±0.2	0.6±0.2
Total daily basal insulin (U/kg/day)	0.4±0.1	0.6±0.1	0.4±0.2	0.3±0.1
Total daily bolus insulin (U/kg/day)	0.4±0.1	0.5±0.1	0.2±0.1	0.3±0.1

Data are mean±SD or median (IQR). Kg = kilogram.

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Figure Legends

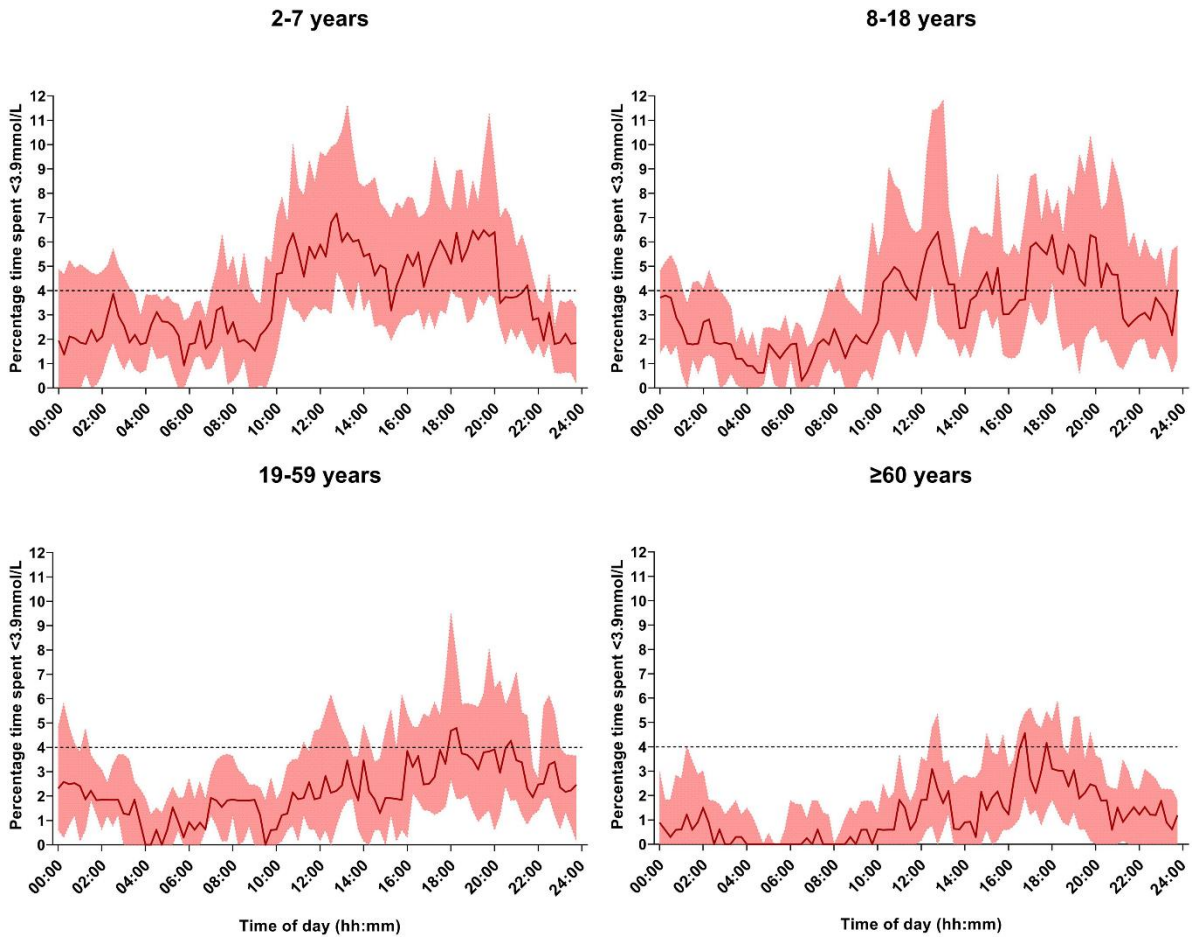

Figure 1. Median percentage time with sensor glucose level <3.9 mmol/l (70 mg/dl) across the four age-groups over 8 weeks (dark red line). The red shaded area indicates the interquartile range. The dashed black line indicates the target percentage time spent below range <4%.

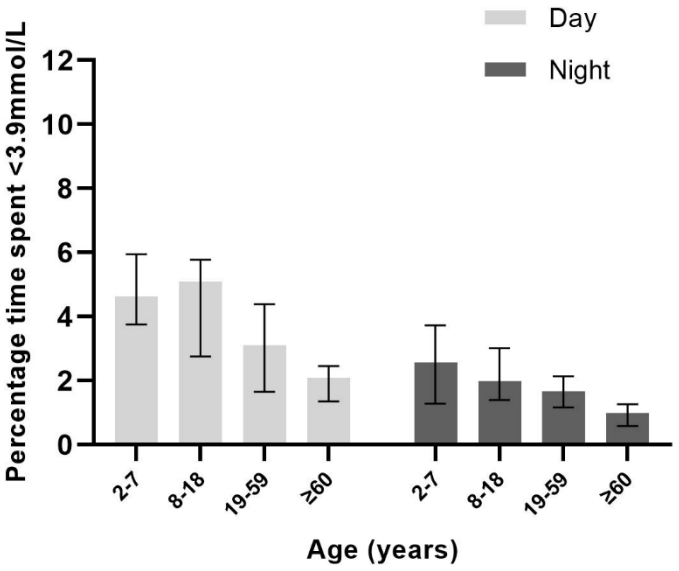

Figure 2. Median percentage time spent with sensor glucose level <3.9 mmol/l (<70 mg/dl) by age-group and time-of-day. Each bar represents an age-group (2-7 years, 8-18 years, 19-59 years, ≥60 years). Data are median (IQR). For daytime (06:00-23:59), P values <0.01 except for 8-18 vs. ≥60 years and 19-59 vs. ≥60 years. For nighttime (midnight-05:59), P values < 0.01 for ≥60 years vs. the other three age-groups.