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BRIEF REPORT

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Day-to-day variability of insulin requirements in the inpatient setting: Observations during fully closed-loop insulin delivery

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Abstract

The aim of this study was to characterize the variability of exogenous insulin requirements during fully closed-loop insulin delivery in hospitalized patients with type 2 diabetes or new-onset hyperglycaemia, and to determine patient-related characteristics associated with higher variability of insulin requirements. We retrospectively analysed data from two fully closed-loop inpatient studies involving adults with type 2 diabetes or new-onset hyperglycaemia requiring insulin therapy. The coefficient of variation quantified day-to-day variability of exogenous insulin requirements during up to 15 days using fully automated closed-loop insulin delivery. Data from 535 days in 67 participants were analysed. The coefficient of variation of day-to-day exogenous insulin requirements was 30% ± 16%, and was higher between nights than between any daytime period (56% ± 29% overnight [11:00 PM to 4:59 AM] compared with 41% ± 21% in the morning [5:00 AM to 10:59 AM], 39% ± 15% in the afternoon [11:00 AM to 4:59 PM] and 45% ± 19% during the evening [5:00 PM to 10:59 PM]; all $P < 0.01$). There is high day-to-day variability of exogenous insulin requirements in inpatients, particularly overnight, and diabetes management approaches should account for this variability.

KEYWORDS
continuous glucose monitoring (CGM), diabetes complications, insulin pump therapy, insulin therapy, observational study, type 2 diabetes

* Charlotte K. Boughton and Aideen Daly contributed equally to this report.

continuous glucose monitoring devices, sensors, and details of communication protocol to facilitate real-time connectivity. LB received financial support from the University Hospital Bern, University of Bern, Swiss National Science Foundation, Grant/Award Number: P1BEP3_165297; and the Swiss Diabetes Foundation

1 | INTRODUCTION

Safe and effective management of diabetes and stress-related hyperglycaemia in hospitalized patients can be challenging because of the impact of metabolic responses to acute illness, inconsistent oral intake and use of nutritional support, scheduled or unscheduled fasting periods, and medications affecting insulin sensitivity, for example, corticosteroids.[1,2] Exogenous insulin requirements may vary considerably from day to day as a result of these factors. To date, characterization of the variability of day-to-day insulin requirements in the inpatient setting has not been reported.

Automated closed-loop insulin delivery systems can be used as a tool to provide an estimate of exogenous insulin requirements. Closed-loop systems incorporate an algorithm to modulate insulin delivery in response to real-time sensor glucose levels, reflecting the amount of insulin required to achieve in-hospital treatment targets.

Fully closed-loop insulin delivery has been evaluated in inpatients with type 2 diabetes or new-onset hyperglycaemia in the non-critical care setting.[3–6] Randomized controlled trials comparing closed-loop insulin delivery with usual care on the general wards have demonstrated superior glycaemic control without increasing the risk of hypoglycaemia, even in patients requiring enteral/parenteral nutrition and haemodialysis.[3–6]

In this retrospective analysis, we quantify the day-to-day variability of exogenous insulin delivery in adult inpatients with type 2 diabetes or new-onset hyperglycaemia during a period of up to 15 days of fully closed-loop insulin delivery.[4,5] We compare patient-related characteristics between those with higher and lower variability of insulin requirements and relationship to glycaemic endpoints.

2 | RESEARCH DESIGN AND METHODS

This retrospective post hoc analysis evaluated closed-loop-directed insulin delivery, as a marker of exogenous insulin requirements, from two multinational randomized controlled trials.[4,5]

Approvals were received from independent research ethics committees and national regulatory authorities in the UK and Switzerland prior to study start. All participants provided written informed consent. Eligible participants were adult inpatients on non-critical care wards (medical or surgical) with type 2 diabetes or new-onset hyperglycaemia requiring subcutaneous insulin therapy and, for one study, there was an additional requirement for nutrition support (enteral/parenteral nutrition). Inpatients with type 1 diabetes were excluded. Only data from participants assigned to receive fully closed-loop insulin delivery were analysed in the present study.

Participants used the FlorenceD2W-T2 closed-loop system comprising a Dana R insulin pump (Diabecare, Seoul, South Korea), the Freestyle Navigator II continuous glucose monitor (Abbott Diabetes Care, Alameda, CA, USA) and a control algorithm device containing the model predictive control algorithm (University of Cambridge, Cambridge, UK) continuously for up to 15 days without any meal announcements or prandial insulin boluses. The participants' usual insulin therapy and/or sulphonylurea medication, if prescribed, was discontinued on the day of closed-loop initialization. All other medications were continued. Standard insulin aspart (Novorapid; Novo Nordisk, Bagsværd, Denmark) was used in one study,[4] and fast-acting insulin aspart (Fiasp; Novo Nordisk) was used in the other.[5]

2.1 | Data analysis and statistical methods

Study participants with ≥4 complete days of closed-loop use were included in the analysis. The coefficient of variation (CV) of exogenous insulin delivery was calculated for each participant to quantify intra-person variability of insulin requirements overall (12:00 AM to 11:59 PM), and during different periods of the day including morning (5:00 AM to 10:59 AM), afternoon (11:00 AM to 4:59 PM), evening (5:00 PM to 10:59 PM) and overnight (11:00 PM to 4:59 AM).

The overall CV was used to stratify participants into tertiles for comparisons of demographics and glycaemic endpoints (closed-loop performance). Pairwise comparisons were made between high and low insulin variability groups. Data were compared using a chi-squared test or one-way analysis of variance, with post hoc analysis using the least significant difference test for pairwise comparisons. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge) and statistical analyses were performed using SPSS, version 27 (IBM Software, Hursley, UK). Data are reported as mean ± SD and P values of <0.05 were considered statistically significant.

3 | RESULTS

Data from 535 inpatient days from 67 study participants were analysed. Baseline demographics (mean ± SD) were: 69% male, age 68 ± 10 years, body mass index 32 ± 8 kg/m^2, baseline glycated haemoglobin (HbA1c) 65 ± 22 mmol/mol (8.1% ± 2.0%), and duration of diabetes 17 ± 13 years. Of those participants included, 31.3%

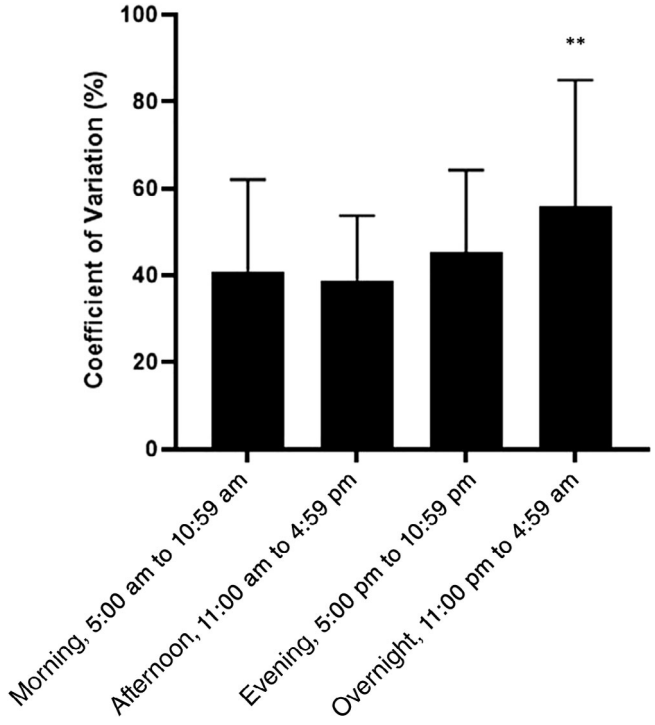

FIGURE 1 Coefficient of variation of insulin requirements during fully closed-loop insulin delivery. Each bar represents a different period of the day. Data are mean ± SD. ** P <0.01

received enteral/parenteral nutrition, 13.4% haemodialysis, and 13.4% corticosteroid therapy during the study period.

The proportion of time in target glucose range between 5.6 and 10.0 mmol/L achieved with fully closed-loop delivery during the period analysed was 67.1% ± 15.1% (mean ± SD), with time above target glucose range (>10.0 mmol/L) 22.5% ± 15.1% and time in hypoglycaemia (<3.9 mmol/L) 0.8% ± 0.8%. Mean sensor glucose was 8.4 ± 1.2 mmol/L and its standard deviation 2.5 ± 0.9 mmol/L. The total daily insulin dose was 60 ± 56 units/d with mean insulin infusion rate 2.4 ± 2.3 units/h.

The between 24-hour period CV of insulin requirements was 30% ± 16%. The CV between night insulin requirements was higher than between any of the daytime periods (overnight [11:00 PM to 4:59 AM] 56% ± 29% vs. morning [5:00 AM to 10:59 AM] 41% ± 21%, afternoon [11:00 AM to 4:59 PM] 39% ± 15%, and evening [5:00 PM to 10:59 PM] 45% ± 19%; all P <0.01). Figure 1 shows the CV of exogenous insulin requirements during the different parts of the day.

The mean closed-loop-directed insulin infusion rates varied throughout the day: 2.9 ± 2.8 units/h during the morning, 3.2 ± 3.9 units/h in the afternoon, 2.3 ± 2.0 units/h in the evening and 1.6 ± 1.8 units/h during overnight periods (between groups P = 0.012).

A post hoc test comparing high and low CV groups demonstrated that inpatients in the highest tertile of insulin variability were younger than those in the lowest tertile (65 ± 10 vs. 71 ± 11 years; P = 0.035). Body mass index, gender, HbA1c, diabetes and insulin duration, use of steroids, and requirement for dialysis or nutrition support were comparable between the high and low insulin variability groups (Table 1).

Participants with high variability of day-to-day insulin requirements had comparable mean glucose (8.3 ± 1.3 vs 8.6 ± 1.5 mmol/L; P = 0.369) and time in target glucose 5.6 to 10 mmol/L (66.9 ± 14.3 vs 66.7% ± 19.4%; P = 0.958) to those with low variability of insulin requirements (Table 1). There was an increase in time spent with sensor glucose below 5.6 mmol/L in those with high CV of exogenous insulin requirements (11.9 ± 6.0 vs. 8.6% ± 4.9%; P = 0.041), but no increase in time spent in hypoglycaemia below 3.9 mmol/L in this group compared to those with low insulin variability (0.79 ± 0.82 vs. 0.71% ± 0.80%; P = 0.690).

4 | DISCUSSION

The present analysis showed considerable variability of day-to-day exogenous insulin requirements during use of a fully automated closed-loop insulin delivery system in inpatients with type 2 diabetes or new-onset hyperglycaemia.

We observed higher variability of insulin requirements between night-time periods (CV of 56%) compared to between daytime periods (CV of 39%-45%), in the context of lower insulin requirements overnight. Identifying higher-risk periods, where increased attention needs to be given to glucose management, is important to prevent adverse glycaemic events in inpatients. The variability of overnight exogenous insulin requirements in people with type 2 diabetes or new-onset hyperglycaemia in the inpatient setting in the present study was even greater than the variability of overnight insulin requirements reported in adults with type 1 diabetes: 56% compared with 31% and 36%.[7,8]

These results enhance our understanding of why attainment of recommended glucose targets during the hospital admission is challenging. The workload associated with regularly adjusting insulin doses to meet treatment goals is a significant burden in the inpatient setting. Inpatient dysglycaemia is a poor prognostic marker, associated with increased morbidity and mortality, length of stay, and healthcare costs.[2] Our observations may help to further understand why, despite frequent capillary blood glucose monitoring and regular insulin dose adjustments, dysglycaemia is common in people with type 2 diabetes and new-onset hyperglycaemia during the hospital admission.[1]

High variability of insulin requirements was associated with lower participant age in our analysis. We hypothesize that this may reflect greater caloric intake in younger inpatients[9] although other reasons may apply. No other demographic factors significantly influenced variability of insulin requirements in our analysis.

The high day-to-day variability of insulin requirements is difficult to overcome with conventional therapeutic tools, multiple daily injections and insulin pumps. Therefore, our results emphasize the importance of advanced technologies such as closed-loop systems to safely and effectively manage inpatient diabetes. The

TABLE 1 Baseline demographics and glycaemic outcomes between different tertiles of variability of exogenous insulin requirements during fully automated closed-loop insulin delivery

	High CV (n = 22)	Medium CV (n = 23)	Low CV (n = 22)	*P* value*
CV of insulin requirements, %	47.5 ± 13.0	27.5 ± 4.7	14.4 ± 3.9	<0.001
Male sex, n (%)	15 (68)	18 (78)	13 (59)	0.382
Age, years	64.6 ± 9.7	69.5 ± 7.7	70.7 ± 10.7	0.035
HbA1c, mmol/mol	69.2 ± 24.0	55.6 ± 10.7	70.2 ± 26.6	0.882
HbA1c, %	8.5 ± 2.2	7.2 ± 1.0	8.6 ± 2.4	0.907
Weight, kg	93.2 ± 20.5	97.3 ± 29.4	109.6 ± 42.4	0.095
BMI, kg/m^2	32.9 ± 8.6	29.9 ± 5.5	34.5 ± 10.1	0.537
Duration of diabetes, years	15.0 ± 13.3	17.7 ± 12.6	18.2 ± 12.6	0.417
Duration of insulin therapy, years	6.8 ± 9.5	8.5 ± 10.2	11.8 ± 9.9	0.099
Preadmission insulin, n (%)	17 (77)	18 (78)	17 (77)	0.955
Steroids, n (%)	3 (14)	4 (17)	2 (9)	0.716
Haemodialysis, n (%)	5 (23)	2 (9)	2 (9)	0.296
Nutrition support, n (%)	5 (23)	10 (44)	6 (27)	0.286
Time spent with glucose, %				
5.6-10.0 mmol/L	66.9 ± 14.3	67.7 ± 11.5	66.7 ± 19.4	0.958
>10.0 mmol/L	21.2 ± 16.2	21.6 ± 11.5	24.8 ± 17.6	0.442
<5.6 mmol/L	11.9 ± 6.0	10.7 ± 4.9	8.6 ± 4.9	0.041
<3.9 mmol/L	0.79 ± 0.82	0.79 ± 0.92	0.71 ± 0.80	0.690
Mean glucose, mmol/L	8.3 ± 1.3	8.3 ± 0.8	8.6 ± 1.5	0.369
SD glucose, mmol/L	2.5 ± 0.8	2.4 ± 0.6	2.5 ± 1.2	0.812
Total insulin dose, units/d	67.2 ± 84.3	50.8 ± 28.7	63.3 ± 39.9	0.710

Note: Data are presented as mean ± SD. **P* value is post hoc test of pairwise comparison of high CV and low CV groups. Glucose data are based on sensor glucose measurements.

Abbreviations: BMI, body mass index; CV, coefficient of variation; HbA1c, glycated haemoglobin; SD, standard deviation.

advantage of automated, algorithm-directed insulin delivery systems is the frequent modulation of insulin delivery according to real-time sensor glucose concentrations, thereby accommodating variability of insulin delivery to achieve glycaemic consistency. We have shown in this analysis that fully closed-loop insulin delivery systems can accommodate highly variable day-to-day insulin requirements without compromising glucose control or increasing the risk of hypoglycaemia.

The strengths of our investigations include the heterogeneity of participants included and the multinational study design, which supports the generalizability of our findings. Limitations include minor differences in study design that were not controlled for, and a relatively short follow-up period. We did not evaluate the impact of individual non-insulin glucose-lowering therapies. The study was not powered to assess the impact of individual factors (dialysis, nutrition support, steroid therapy) on variability of insulin requirements.

In summary, there is high day-to-day variability of exogenous insulin requirements in the inpatient population, particularly overnight. Diabetes management approaches should account for this variability and consider adoption of closed-loop systems in the inpatient setting.

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CONFLICT OF INTEREST

H.T. reports having received research support and speaker honoraria from Dexcom. S.H. serves as a member of Sigma (Dexcom) and Medtronic advisory boards, is a director of Ask Diabetes Ltd, providing training and research support in healthcare settings, and reports having received training honoraria from Medtronic and Sanofi. M.E.W. reports receiving licence fees from B. Braun, patents related to closed-loop, and being a consultant at CamDiab. M.L.E. reports having received speakers/writers' fees, acted on advisory board and/or had research collaborations with/acted as a triallist for Eli Lilly, NovoNordisk, Sanofi, Medtronic, Dexcom, Roche, Astra Zeneca, Zucara, Boehringer Ingelheim, Abbott Diabetes Care, NGM Pharma, Imcyse and Ypsomed. R.H. reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving fees from B. Braun and Abbott Diabetes Care; patents related to closed-loop, and being director at CamDiab. C.K.B., A.D., L.B., D.H., A.V., Y.R. and A.P.C. declare that no competing financial interests exist.

AUTHOR CONTRIBUTIONS

C.K.B. and R.H. designed the analysis. R.H., C.K.B., L.B., S.H., M.E.W., M.L.E. and A.P.C. co-designed the studies. R.H. designed the control algorithm. C.K.B., L.B., H.T. and S.H. were responsible for screening and enrolment of participants, arranged informed consent from the participants and provided patient care. C.K.B., A.D. and R.H. carried out data analysis. R.H., C.K.B., A.D., D.H., Y.R. and L.B. contributed to the interpretation of the results. C.K.B., A.D. and R.H. wrote the manuscript. All authors critically reviewed the report. C.K.B. and R.H. had full access to all of the data in the studies and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors decided to publish the paper. No writing assistance was provided.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. NHS Digital. National Diabetes Inpatient Audit (NaDIA) 2019. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-inpatient-audit/2019 (Accessed 27 January 2021).
2. Dhatariya K, Corsino L, Umpierrez GE. Management of diabetes and hyperglycemia in hospitalized patients. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*. South Dartmouth, MA: MDText.com, Inc; 2020.
3. Thabit H, Hartnell S, Allen JM, et al. Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. *Lancet Diabetes Endocrinol*. 2017;5(2):117-124.
4. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. *N Engl J Med*. 2018;379(6):547-556.
5. Boughton CK, Bally L, Martignoni F, et al. Fully closed-loop insulin delivery in inpatients receiving nutritional support: a two-Centre, open-label, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(5):368-377.
6. Bally L, Gubler P, Thabit H, et al. Fully closed-loop insulin delivery improves glucose control of inpatients with type 2 diabetes receiving hemodialysis. *Kidney Int*. 2019;96(3):593-596.
7. Dovc K, Boughton C, Tauschmann M, et al. Young children have higher variability of insulin requirements: observations during hybrid closed-loop insulin delivery. *Diabetes Care*. 2019;42(7):1344-1347.
8. Ruan Y, Thabit H, Leelarathna L, et al. Variability of insulin requirements over 12 weeks of closed-loop insulin delivery in adults with type 1 diabetes. *Diabetes Care*. 2016;39(5):830-832.
9. Giezenaar C, Chapman I, Luscombe-Marsh N, Feinle-Bisset C, Horowitz M, Soenen S. Ageing is associated with decreases in appetite and energy intake—a meta-analysis in healthy adults. *Nutrients*. 2016;8(1):28.

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