Variability of insulin requirements over 12-weeks of closed-loop insulin delivery in adults with type 1 diabetes

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Running title: Variability of insulin requirements

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Word count:	930
Abstract:	150
Figures:	1
Tables:	0
Supplemental online material:	1

Abstract

Objective

To quantify variability of insulin requirements during closed-loop insulin delivery.

Research Design and Methods

We retrospectively analyzed overnight, daytime and total daily insulin amounts delivered during multicenter closed-loop trial involving 32 adults with type 1 diabetes. Participants applied hybrid day-and-night closed-loop under free-living home conditions over 12 weeks. The coefficient of variation was adopted to measure variability of insulin requirements in individual subjects.

Results

Data were analyzed from 1,918 nights, 1,883 daytime periods and 1,564 total days characterized by closed-loop use over 85% of time. Variability of overnight insulin requirements [coefficient of variation 31%(4), mean(SD)] was nearly twice as high as variability of total daily requirements [17%(3),p<0.001] and was also higher than variability of daytime insulin requirements [22%(4), p<0.001].

Conclusions

Overnight insulin requirements were significantly more variable than daytime and total daily amounts. This may explain why some people with type 1 diabetes report frustrating variability in morning glycemia.

INTRODUCTION

Closed-loop insulin delivery is an emerging treatment modality for people with type 1 diabetes (1). Multi-week free-living overnight or day-and-night home investigations demonstrated improved glycemic control and reduced hypoglycemia with hybrid closed-loop compared to conventional sensor-augmented pump therapy (2-4). Insulin delivery modulated by closed-loop systems reflects the amount of insulin required in real-time which may vary from night-to-night and from day-to-day. The present investigation measures night-to-night and day-to-day variability of insulin requirements in adults with type 1 diabetes over 12 weeks of closed loop insulin delivery (2).

RESEARCH DESIGN AND METHODS

We retrospectively analyzed overnight (23:00 to 07:00), daytime (07:00 to 23:00) and total daily (midnight to midnight) insulin delivery during closed-loop period in a multicenter (United Kingdom, Germany and Austria), randomized cross-over study involving 32 subjects with type 1 diabetes and conducted in free-living home settings (2). Subjects underwent 4 to 6 weeks optimization of insulin pump therapy using real-time continuous glucose monitoring with trained pump educators before randomization. Day-and-night closed-loop insulin delivery was then applied over 12 weeks using a hybrid approach, in which participants additionally administered prandial insulin using the standard bolus wizard.

We calculated relative overnight, relative daytime and relative total daily insulin requirements defined as the percentage of the total amount of insulin administered by closed-loop during the relevant time period, over the optimized insulin pump

amounts determined prior to the start of closed-loop period (Calculating variability of insulin requirements, Supplemental Appendix). For each subject, an individual coefficient of variation of overnight, daytime and total daily insulin requirements over 12 weeks was calculated to represent variability of insulin requirements. A repeated measures least-square regression model was used to contrast variability (the coefficient of variation) of overnight, daytime and total daily requirements. Post-hoc analysis using Tukey test was used for pairwise comparisons. A linear mixed-effect regression analysis was used to relate the individual coefficient of variation of insulin requirements (dependent variable) and subjects' baseline characteristics (independent predictors: gender, age, BMI, duration of diabetes, duration of pump use and HbA1c at the start of closed-loop use). Statistical analyses were performed using SPSS, version 21 (IBM Software, Hampshire, U.K.). Data are reported as mean(standard deviation) unless stated otherwise. *P* values less than 0.05 were considered statistically significant.

RESULTS

We analyzed data from 1,918 nights, 1,883 daytime periods and 1,564 total days characterized by closed-loop use over 85% of time in 32 adults [male/female 17/15, age 39.9(9.5) years, BMI 25.4(4.4) kg/m^2, duration of diabetes 21.2(9.3) years, duration of pump use 7.9(6.0) years, HbA1c at the start of closed loop use 7.6%(0.8), 60(9) mmol/mol, HbA1c at the end of closed loop use 7.3%(0.8), 56(9) mmol/mol]. Figure 1 shows individual overnight, daytime and total daily insulin requirements ranging from approximately 50 to 300%, 50 to 200% and 70 to 200%, respectively, relative to baseline requirements. The coefficients of variation differed between the three periods ($p<0.001$). Overnight insulin requirements were 14 percentage points higher than the coefficient variation of total daily requirements [31%(4) vs. 17%(3),

p<0.001] and 9 percentage points higher than daytime requirements [31%(4) vs. 22%(4), *p*<0.001] (Supplemental Figure S1). Supplemental Table S1 reports the regression coefficients of baseline predictors in the mixed-effect regression analyses. The coefficient of variation of overnight insulin requirements in male subjects was 3.7% higher than in females (*p*=0.03). No other relationship was observed.

CONCLUSIONS

To our knowledge, this is the first study to report on the variability of overnight, daytime and total daily insulin requirements over a prolonged period in adults with type 1 diabetes. We report highly variable overnight insulin requirements (from half to three-fold of the baseline amounts) and to a lesser extent during daytime and over 24 hours (from half to two-fold of the baseline amounts) over 12 weeks of free-living home use of closed-loop insulin delivery.

Potential factors contributing to variability of overnight insulin requirements include the composition of evening meal (5), the prolonged effect of daytime exercise on glucose turnover (6), variable insulin absorption (7) encompassing the effect of infusion set change (8) and lipohypertrophy (9), and changes in insulin sensitivity induced by stress, intercurrent illness (10) and menstrual cycle phases in women (11). We observed mean overnight insulin requirements 31% higher than baseline optimized insulin dose (data not shown), despite weekly continuous-glucose-monitoring guided optimization of insulin pump settings by experienced healthcare professionals. Concerns related to hypoglycemia especially overnight (12) may have limited further insulin therapy intensification underscoring the need for closed-loop insulin delivery when insulin requirements are highly variable.

Predictors of variability of insulin requirements may support clinical management and inform treatment goals. The regression analysis demonstrated a potential gender cofactor with a surprisingly greater overnight variability observed in male compared to female participants despite a documented effect of menstrual cycle phases in

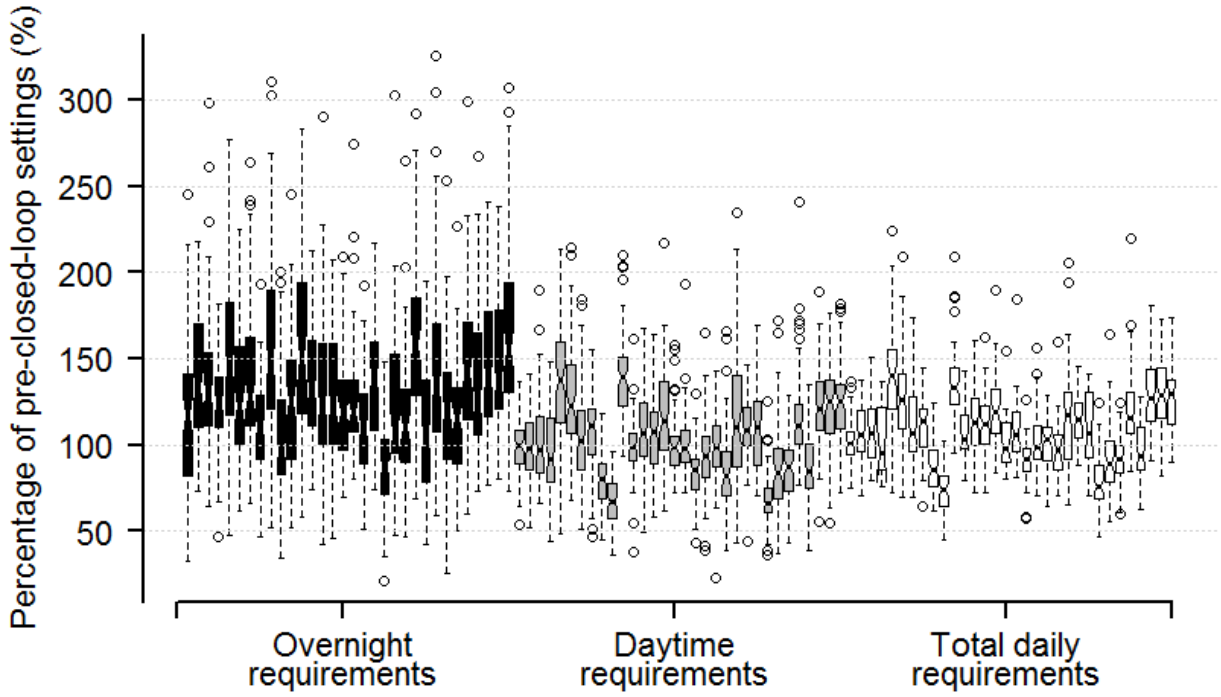
women (11).The notable gender differences is unexpected and warrant further investigations to exclude the possibility of chance finding.

During the past decade, clinical trials of closed-loop insulin delivery have transitioned from controlled settings in research facilities to free-living home conditions with improvements demonstrated in time spent in the target glycemic range, mean glucose as well as reduced hypoglycemia (2-4). This was achieved despite or more appropriately because of variable overnight and total daily insulin requirements, as reported in the present study. Closed-loop systems with adaptive control algorithms have the advantage of autonomously and continually assessing insulin requirements addressing the unmet need of managing day-to-day and within-day variability commonly observed in clinical practice. The present analysis pinpoints the reasons why people with type 1 diabetes benefit from closed-loop insulin delivery and indicates that greatest benefit may apply overnight when insulin requirements are most variable and real-time adaptive insulin delivery is most desirable.

The main strength of the present study is the quantification of variability of insulin requirements derived from data collected over prolonged period under free-living conditions reflecting participants' insulin needs in real-life. Factors leading to night-to-night and day-to-day differences in insulin requirements are still not fully understood. Potential predictors such as the daily level and types of physical activities (13) and meal composition were not available, which is a limitation of the present analyses.

In conclusion, insulin requirements assessed by closed loop insulin delivery during the overnight period were significantly more variable than daytime and total daily amounts. This may explain why some people with type 1 diabetes report frustrating variability in morning glycemia.

Figure 1. Insulin requirements relative to baseline amounts during closed-loop insulin delivery. Each box plot represents individual insulin requirements over 12 weeks of closed-loop insulin delivery (black box plots: overnight (23:00 to 07:00); grey box plots: daytime (07:00 to 23:00); white box plots: midnight-to-midnight) relative to insulin delivery prior to initiating closed loop (N=32). The coefficients of variation of overnight, daytime and total daily insulin requirements are 31%(4) vs. 22%(4) vs. 17%(3) (*p* < 0.001 for pairwise comparisons between any two time periods).



Funding

Seventh Framework Programme of the European Union (ICT FP7- 247138). Additional support for the Artificial Pancreas work by JDRF, National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award (100574/Z/12/Z). Abbott Diabetes Care supplied discounted continuous glucose monitoring devices, sensors, and communication protocol to facilitate real-time connectivity.

Duality of interest

RH reports having received speaker honoraria from Minimed Medtronic, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Eli Lilly, Novo Nordisk and Merck, receiving license fees from BBraun and Medtronic; and having served as a consultant to BBraun and Profil. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. MLE reports having received speaker honoraria from Abbott Diabetes Care, Novo Nordisk and Animas, serving on advisory panels for Novo Nordisk, Abbott Diabetes Care, Medtronic, Roche and Cellnovo and holding stock options in Cellnovo. SH serves as a consultant for Novo-Nordisk and for the ONSET group, and reports having received speaker/training honoraria from Medtronic. RH and MEW report patents and patent applications. JKM reports having received speaker honoraria from DexCom, NovoNordisk and Roche Diagnostics, and serving on advisory panel for Sanofi and Boehringer Ingelheim. TRP is an advisory board member of Novo Nordisk A/S, a consultant for Roche, Novo Nordisk A/S, Eli Lilly & Co, Infineon, Carnegie Bank and on speaker's bureau of Novo Nordisk A/S and Astra Zeneca. YR, HT, LL, SD, CB, MH, HK, and SA declare no competing financial interests exist.

Author contributions

RH had full access to all of the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analysis. RH coordinated the study. RH, MLE, LL, CB, SA, HT, and MEW co-designed the study. HT, SH, SD, JKM, MH, HK, and JP were responsible for screening and enrolment of participants, and arranged informed consent from the participants. HT, SH, SD, JKM, MH, and HK provided patient care and/or took samples. YR and RH carried out data analysis. YR and RH wrote the manuscript. All authors critically reviewed the report.

Acknowledgement

We are grateful to study volunteers for their participation. We acknowledge support by the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility. Jasdip Mangat and John Lum (Jaeb Center) supported development and validation of the closed-loop system. Josephine Hayes (University of Cambridge) provided administrative support. Karen Whitehead (University of Cambridge) provided laboratory support. We acknowledge support by the staff at Profil Institut; Krisztina Schmitz-Grozs provided support as a research physician, Martina Haase supported the study as an insulin pump expert, and Maren Luebkert, Kirstin Kuschma and Elke Przetak provided administrative, coordinating and documentation support.

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