Variability of Insulin Requirements Over 12 Weeks of Closed-Loop Insulin Delivery in Adults With Type 1 Diabetes

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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 a multicenter closed-loop trial involving 32 adults with type 1 diabetes. Participants applied hybrid day-and-night closed-loop insulin delivery 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 (mean [SD] coefficient of variation 31% [4]) 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.

Closed-loop insulin delivery is an emerging treatment modality for people with type 1 diabetes (1). Multiweek free-living overnight or day-and-night home investigations demonstrated improved glycemic control and reduced hypoglycemia with hybrid closed-loop compared with 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 (2300–0700 h), daytime (0700–2300 h), and total daily (midnight to midnight) insulin delivery during a closed-loop period in a multicenter (U.K., Germany, and Austria), randomized crossover study involving 32 subjects with type 1 diabetes and conducted in free-living home settings (2).

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Subjects underwent 4–6 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 with use of 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 delivery during the relevant time period over the optimized insulin pump amounts determined prior to the start of closed-loop period (see "Calculating Variability of Insulin Requirements" in Supplementary Data). 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 squares regression model was used to contrast variability (the coefficient of variation) of overnight, daytime, and total daily requirements. Post hoc analysis using the 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: sex, age, BMI, duration of diabetes, duration of pump use, and HbA_{1c} 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 (SD) unless stated otherwise. *P* values <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; HbA_{1c} at the start of closed-loop use 7.6% [0.8], 60 [9] mmol/mol; and HbA_{1c} 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 ~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 of 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], $P < 0.001$) (Supplementary Fig. 1). Supplementary Table 1 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.

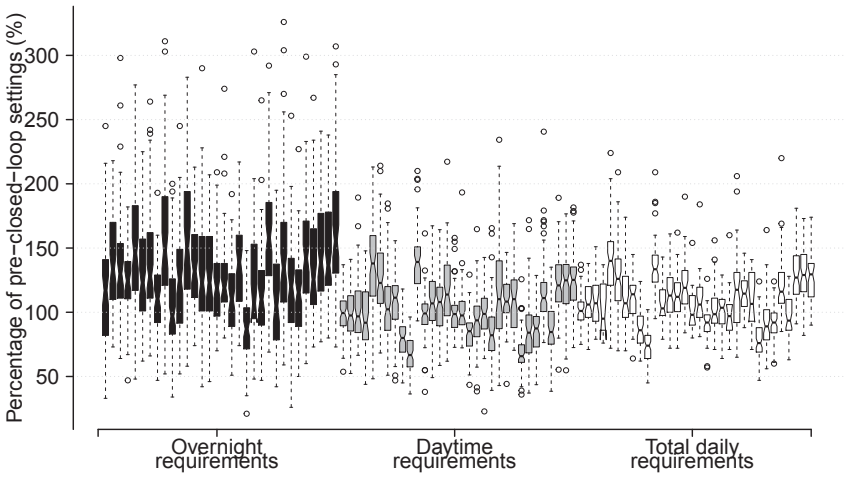

Figure 1—Insulin requirements relative to baseline amounts during closed-loop insulin delivery. Each box plot represents individual insulin requirements over 12 weeks of closed-loop insulin delivery (black box plots, overnight [2300–0700 h]; gray box plots, daytime [0700–2300 h]; white box plots, midnight 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), respectively ($P < 0.001$ for pairwise comparisons between any two time periods).

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 threefold of the baseline amounts) and to a lesser extent during daytime and over 24 h (from half to twofold 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 the 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 health care 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 sex cofactor, with a surprisingly greater overnight variability observed in male compared with female participants despite a documented effect of menstrual cycle phases in women (11). The notable sex 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 and 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 current 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 current study is the quantification of variability of insulin requirements derived from data collected over a 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.

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Duality of Interest. S.H. serves as a consultant for Novo Nordisk and for the ONSET study group and reports having received speaker/training honoraria from Medtronic. M.E.W. and R.H. report patents and patent applications related to closed-loop insulin delivery. M.E.W. has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. M.L.E. 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. J.K.M. reports having received speaker honoraria from Dexcom, Novo Nordisk, and Roche Diagnostics and serving on an advisory panel for Sanofi and Boehringer Ingelheim. T.R.P. is an advisory board member of Novo Nordisk A/S; a consultant for Roche, Novo Nordisk A/S, Eli Lilly, Infineon, and Carnegie Bank; and on the speaker's bureau of Novo Nordisk A/S and AstraZeneca. R.H. 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. No other potential conflicts of interest relevant to this article were reported.

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