Young Children Have Higher Variability of Insulin Requirements: Observations During Hybrid Closed-Loop Insulin Delivery

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OBJECTIVE

To quantify age-related variability of insulin needs during day and night closed-loop insulin delivery.

RESEARCH DESIGN AND METHODS

We retrospectively analyzed data from hybrid closed-loop studies involving young children (1–6 years old, $n = 20$), children (7–12 years, $n = 21$), adolescents (13–17 years, $n = 15$), and adults (>18 years, $n = 58$) with type 1 diabetes. The coefficient of variation quantified variability of insulin needs during 3 weeks of unrestricted-living hybrid closed-loop use.

RESULTS

Data from 2,365 nights and 2,367 days in 114 participants were analyzed. The coefficient of variation of insulin delivery was higher in young children compared with adults (mean difference at nighttime 10.7 percentage points [95% CI 2.9–18.4], $P = 0.003$; daytime 6.4 percentage points [95% CI 2.0–10.9], $P = 0.002$) and compared with adolescents (mean difference at nighttime 10.2 percentage points [95% CI 0.0–20.4], $P = 0.049$; daytime 7.0 percentage points [95% CI 1.1–12.8], $P = 0.014$).

CONCLUSIONS

Diabetes management in young children is complicated by higher variability in insulin requirements, supporting fast-track clinical practice adoption of closed-loop in this vulnerable population.

NOVEL COMMUNICATIONS IN DIABETES

With increasing application of insulin pump therapy and continuous glucose monitors, hybrid closed-loop has become a feasible treatment modality for people with type 1 diabetes (1,2). Apart from manual meal-time boluses, insulin delivery is autonomously modulated by a control algorithm based on real-time sensor glucose values.

Insulin delivery may vary considerably from day to day and night to night due to varying activity levels, insulin set-changes, meal timings and composition, and other factors (3,4). To date, the association between age and insulin variability has not been assessed. In the present analysis, we investigate whether insulin requirements may be more variable in younger age.

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RESEARCH DESIGN AND METHODS

We retrospectively analyzed closed-loop insulin delivery during the first 3 weeks of unrestricted-living hybrid closed-loop use in four multicenter, multinational (Austria, Germany, Luxembourg, U.K., and U.S.), randomized clinical trials (5–8). Participants aged 1–65 years were enrolled.

Study participants and/or parents/caregivers of participants signed informed consent; in line with local ethics committee recommendations, written assent was obtained from minors whenever possible. The studies were approved by independent research ethics committees (independent review boards in the U.S.) and national regulatory authorities.

Inclusion criteria included type 1 diabetes diagnosis (World Health Organization criteria) for a minimum of 6 months, insulin pump therapy for more than 3 months, and total daily dose of insulin $<$2 IU/kg/day. Inclusion glycated hemoglobin (measured locally) varied between studies; upper limit was 10% (86 mmol/mmol) in two studies (4,7) and 11% (97 mmol/mol) in the other two studies (6,7). Lower limit was 7.5% (58.5 mmol/mol) in two studies (5,8), and in two studies there was no lower threshold (6,7).

Closed-Loop Devices

Closed-loop systems (University of Cambridge) (Supplementary Figs. 1 and 2) comprised a model predictive control treat-to-target algorithm residing on a smartphone. Hybrid closed-loop insulin delivery was applied day and night with manual boluses at meal time (see Supplementary Data for details).

Data Analysis and Statistical Methods

For each participant, the coefficient of variation of insulin delivery between midnight and 0559 h was calculated using data collected over 3 weeks of hybrid closed-loop use to quantify night-by-night intraperson variability of insulin requirements (combining prandial, correction, and basal insulin delivered). Similar calculations were made for the daytime period between 0600 h and 2359 h.

Analyses were stratified according to four age-groups: young children (1–6 years), children (7–12 years), adolescents (13–17 years), and adults (18 years and older). The groups were compared using the one-way ANOVA with post hoc analysis using the Tukey test for pairwise comparisons. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge), and statistical analyses were performed using SPSS, version 25 (IBM Software, Hampshire, U.K.). Data are reported as mean $\pm$ SD. P values $<$0.05 were considered statistically significant.

RESULTS

We analyzed data from 2,365 nights and 2,367 days collected from 114 participants aged between 1 and 65 years: 20 children aged 1–6 years (HbA_{1c} 7.3 $\pm$ 0.7% [56 $\pm$ 7.7 mmol/mol], total insulin delivered [TDD] 0.90 $\pm$ 0.21 units/kg), 21 children aged 7–12 years (HbA_{1c} 8.4 $\pm$ 0.7% [68 $\pm$ 7.7 mmol/mol], TDD 1.01 $\pm$ 0.21 units/kg), 18 adolescents aged 13–17 years (HbA_{1c} 8.2 $\pm$ 0.5% [66 $\pm$ 5.5 mmol/mol], TDD 0.94 $\pm$ 0.19 units/kg), and 58 adults aged 18 years and older (HbA_{1c} 8.4 $\pm$ 0.6% [68 $\pm$ 6.6 mmol/mol], TDD 0.62 $\pm$ 0.15 units/kg). The time when sensor glucose was in target glucose range between 70 and 180 mg/dL was similar across all age-groups (at $\sim$70%) (Supplementary Tables 1–3).

Figure 1 shows the coefficient of variation of insulin delivery for the four age-groups. The coefficient of variation of nighttime insulin delivery for young children was 10.7 percentage points higher compared with adults (95% CI 2.9–18.4, $P = 0.003$), and 10.2 percentage points higher compared with adolescents (95% CI 0.0–20.4, $P = 0.049$). Similar differences were observed during the daytime period, with the coefficient of variation 6.4 percentage points higher in young children compared with adults (95% CI 2.0–10.9, $P = 0.02$) and 7.0 percentage points higher compared with adolescents (95% CI 1.1–12.8%, $P = 0.014$). There was no difference in the coefficient of variation for the daytime period ($P = 0.73$) and the nighttime period ($P = 0.74$) based on age at diagnosis for those aged 13 years and older (Supplementary Table 4).

Male participants had 11.5 percentage points greater insulin variability during nighttime than females ($P = 0.004$), whereas there was no sex-related difference during daytime. The difference was statistically significant in the adult age-group ($P = 0.001$), but not in the other.

CONCLUSIONS

The current study reports on the effect of age on the variability of insulin needs during unrestricted-living hybrid closed-loop use. We observed a clinically significant increase in the variability of more than 10 percentage points during the nighttime period and, to a lesser degree, during the daytime period in young children compared with adolescents and adults. Our observations may inform clinical practice.

For people with type 1 diabetes, the burden of regularly adjusting insulin therapy to meet treatment goals is a significant challenge, especially in the pediatric population due to varying spontaneous activity levels, developmental and hormonal changes, varying lifestyle modalities, and other factors. Our observations may help to explain why, despite frequent insulin dose adjustments, dysglycemia and a higher risk of nocturnal hypoglycemia are common and contribute to a lower quality of life for young children with type 1 diabetes and their families (9,10).

One possible explanation for the observed difference in the variability of insulin needs could be more rapid and complete depletion of endogenous insulin and dysregulation of glucagon secretion because of more extensive β-cell destruction with early disease onset (11,12). However, our results indicate

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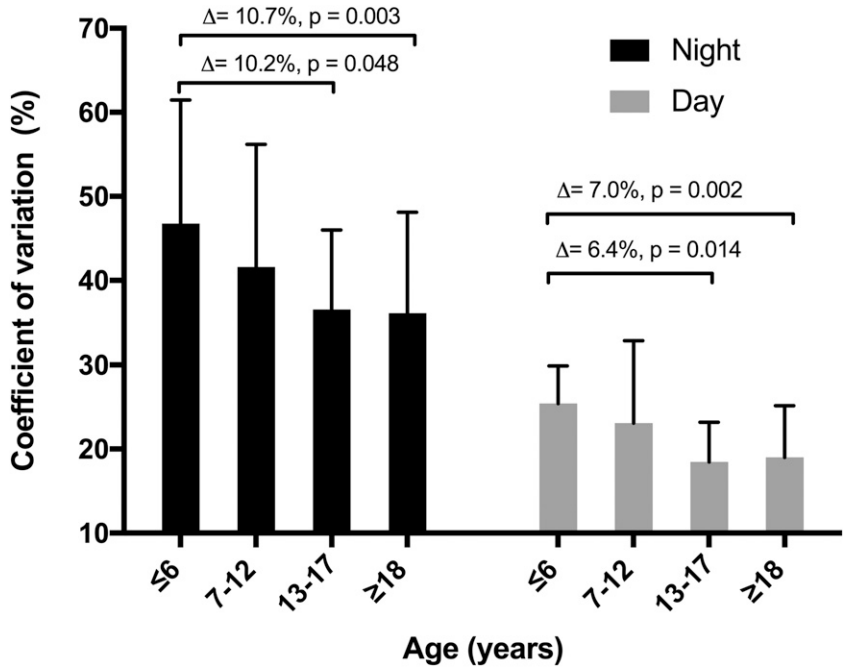

Figure 1—The coefficient of variation for insulin requirements during hybrid closed-loop insulin delivery. Each bar represents an age-group (young children, children, adolescents, and adults); black bars denote nighttime (0000–0559 h) and gray bars daytime (0600–2359 h) periods. Data are mean ± SD.

that actual age rather than age at diagnosis affects variability of insulin requirements, and thus it is likely that unpredictable activity levels, varying meal intake, and lower insulin needs are contributory.

The night-by-night variability of insulin needs might be 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 manage diabetes in the vulnerable group of young children.

We previously observed a significantly higher variability of insulin delivered in adults with type 1 diabetes during the nighttime period, compared with the daytime period (3). Although a similar difference was observed in the current study, the comparison is confounded by the shorter nighttime period. During daytime, prandial boluses can be delivered as part of a standardized diabetes management plan unlike nighttime insulin, which is directed solely by sensor glucose during closed-loop insulin therapy, explaining at least in part the observed differences.

Variability of insulin delivered during nighttime, but not daytime, was greater in male compared with female participants, in keeping with previous study findings (3). This difference was due to differences in the adult age-group and warrants further investigations.

The strengths of our investigations include the broad age range of participants between 1 and 65 years and the multicenter, multinational, unrestricted-living study design without remote monitoring, which supports the generalizability of our findings. Limitations include the use of two closed-loop systems, minor differences in study designs, and a relatively short follow-up period, none of which affects the main study findings.

In summary, insulin needs are more variable in young children compared with adolescents and adults, complicating the attainment of optimal glucose control and increasing the risk of dysglycemia. Young children may benefit to a greater extent from hybrid closed-loop systems, and larger and longer clinical trials are warranted in this vulnerable population.

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Duality of Interest. M.T. has received speaker honoraria from MiniMed Medtronic and Novo Nordisk. M.L.E. has received speaker honoraria from Abbott Diabetes Care, Novo Nordisk, and Animas; has served on advisory panels for Novo Nordisk, Abbott Diabetes Care, Medtronic, Roche, and Cellnovo; and holds stock options in Cellnovo. E.F.-R. has received speaker honoraria from Eli Lilly and Company and Medtronic. S.H. has received speaker honoraria from Eli Lilly and Company and Sanofi. T.K. has received speaker honoraria from Abbott Diabetes Care, Sanofi, Aegerion, and Merck Serono and is a member of the advisory board for Abbott Diabetes Care. L.L. has received speaker honoraria from Minimed Medtronic, Animas, Sanofi, and Novo Nordisk and is serving on an advisory panel for Animas Minimed Medtronic and Novo Nordisk. T.R.P. is an advisory board member of Novo Nordisk A/S and a consultant for Roche, Novo Nordisk A/S, Eli Lilly and Company, Infineon, and Carnegie Bank and is on the speakers' bureau for Novo Nordisk A/S and AstraZeneca. B.R.-M. has received speaker/advisory board honoraria from Medtronic, Roche, Menarini, and Eli Lilly and Company. V.N.S. has received speaking fees from Dexcom Inc. The employer of V.N.S. has received research funding from T1D Exchange and Sanofi. M.E.W. has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. R.H. has received speaker honoraria from MiniMed Medtronic, Eli Lilly and Company, B. Braun, and Novo Nordisk; has served on an advisory panel for Eli Lilly and Company; and has received license fees from B. Braun and Medtronic. M.E.W. and R.H. report patents and patent applications. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.D., C.B., and M.E.W. performed data analysis. K.D., C.B., M.E.W., and R.H. wrote the manuscript. K.D. and R.H. codesigned the analysis. C.B., M.T., H.T., L.B., J.M.A., S.A., C.d.B., R.M.B., F.C., A.C., D.E., E.F.-R., S.H., T.K., L.L., T.R.P., B.R.-M., and V.N.S. were responsible for screening and enrollment of participants, arranged informed consent from the participants, and provided patient care and/or took samples. M.T., C.L.A., D.B.D., M.L.E., M.E.W., and R.H. codesigned the clinical studies. R.H. designed the control algorithm. K.D., C.B.,

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