Fully closed-loop insulin delivery improves glucose control of inpatients with type 2 diabetes receiving hemodialysis

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Inpatient diabetes management of those on hemodialysis poses a major challenge. In a post hoc analysis of a randomized controlled clinical trial, we compared the efficacy of fully automated closed-loop insulin delivery vs. usual care in patients undergoing hemodialysis while in hospital. Compared to control patients receiving conventional subcutaneous insulin therapy, those patients receiving closed-loop insulin delivery significantly increased the proportion of time when a continuous glucose monitor was in the target range of 5.6-10.0 mmol/l by 37.6 percent without increasing the risk of hypoglycemia. Thus, closed-loop insulin delivery offers a novel way to achieve effective and safe glucose control in this vulnerable patient population.

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The prevalence of diabetes is increasing globally, as is the number of people with diabetes requiring hemodialysis.[1,2] Glucose management in this population imposes challenges on both patients and health care professionals. End-stage renal disease and hemodialysis predispose these patients to both hypo- and hyperglycemia,[3] which are associated with adverse medical outcomes.[4,5] The situation is aggravated when patients are admitted to the hospital due to acute illness.[6] Optimal insulin dosing regimens are difficult to establish given the altered glucose metabolism and insulin kinetics in this population.[7,8] Hence, glucose management may be better facilitated by an algorithm-driven insulin therapy, also known as closed-loop insulin delivery or artificial pancreas, which is an emerging therapeutic approach combining continuous glucose monitoring with insulin pump therapy to achieve a more physiological means of replacing insulin.[9] The role of the control algorithm is to continuously modulate insulin delivery based on real-time sensor glucose values, thereby responding to the inherent variability of insulin requirements. The closed-loop system used in the present study incorporates a control algorithm that is initialized based on the subject's body weight and estimated total daily insulin dose, and calculates the required insulin infusion rate, aiming at a target glucose level between 5.8 and 7.2 mmol/l by continuously adapting model parameters.[10]

We hypothesized that fully closed-loop insulin delivery improves glycemic control without increasing the risk of hypoglycemia in inpatients with type 2 diabetes undergoing hemodialysis. Here, we report a *post hoc* analysis in 17 such inpatients who took part in a randomized parallel-design study.[11] The aim of the original study (n = 136) was to assess the efficacy and safety of fully automated closed-loop insulin delivery in comparison with conventional insulin therapy at non–critical care units irrespective of underlying pathophysiology.

RESULTS

Study population

Baseline characteristics were comparable between closed-loop versus control subjects, with mean values as follows: 77%

versus 63% male; age 73 years (SD: 8) versus 67 years (SD: 10); body mass index 31.2 kg/m^2 (SD: 6.5) versus 32.8 kg/m^2 (SD: 6.9); glycated hemoglobin 7.1% (SD: 0.6) versus 6.9% (SD: 1.5); diabetes duration 25 years (SD: 13) versus 28 years (SD: 7); total daily insulin dose 42 U/24 h (SD: 25–55) versus 44 U/24 h (SD: 30–69). At recruitment, none of the closed-loop and 4 of the control participants received adjunctive anti-diabetic treatment (all dipeptidyl peptidase–4 inhibitors, with one patient additionally receiving metformin and the other glucagon-like peptide [GLP]-1 receptor agonist therapy). Participants were followed for up to 8.0 days (SD: 3.1) and 7.7 days (SD: 4.8) in the closed-loop and control groups, respectively, and they underwent 4.2 (SD: 1.5) and 3.6 (SD: 2.5) hemodialysis sessions (both differences nonsignificant).

Glycemic control and insulin dose

The proportion of time spent in the target glucose range, which was between 5.6 and 10 mmol/l, was significantly greater in the closed-loop group compared with the control group (69.0% [SD: 12.0] vs. 31.5% [SD: 13.5], respectively; difference 37.6% [SD: 6.2; 95% confidence interval 24.4 to 50.8]; $P < 0.001$; primary endpoint; Table 1). The mean sensor glucose level was significantly lower in the closed-loop group than in the control group (8.1 mmol/l [SD: 0.6] vs. 11.0 mmol/l [SD: 2.3]; difference 2.9 mmol/l [SD: 0.8; 95% confidence interval 1.2 to 4.6]; $P = 0.003$). The proportion of time spent at concentrations above the target range (>10 mmol/l) was significantly lower in the closed-loop group (difference 37.2% [SD: 9.2; 95% confidence interval 17.7 to 56.9]; $P = 0.001$), whereas the time spent at concentrations lower than the target range (<5.6 mmol/l) did not differ between groups ($P = 0.96$). Time spent at concentrations lower than 3.0 mmol/l, as well as the burden of hypoglycemia measured by area under the curve less than 3.0 mmol/l, was low and similar between groups ($P = 0.82$ and $P = 0.89$, respectively). Total daily insulin dose did not differ between groups ($P = 0.41$). Glucose variability, as measured by SD of sensor glucose was significantly reduced compared with conventional insulin therapy ($P = 0.012$). The coefficient of variation of sensor glucose between 24-hour periods was significantly lower in the closed-loop group than in the control group ($P = 0.008$). Twenty-four-hour sensor glucose and insulin delivery profiles are shown in Figure 1. Hypoglycemic (<3.5 mmol/l) or hyperglycemic (>20 mmol/l) events based on capillary glucose were detected, respectively, in 1 control and in none of the closed-loop patients, and in 1 closed-loop and 2 control patients, although none of them had concomitant ketonemia.

DISCUSSION

Increasing evidence shows that closed-loop insulin delivery is superior to conventional insulin treatment in different target groups, such as children, adolescents, pregnant women with type 1 diabetes, and more recently, inpatients with type 2 diabetes.[11–13] Glucose management in hospitalized patients undergoing hemodialysis is particularly challenging, and until now, whether a control algorithm can accommodate their specific requirements has been unclear. For the first time, we have shown here that a fully automated closed-loop system clearly improves glucose control in this vulnerable population.

The closed-loop system increased time in the glycemic target range (5.6–10.0 mmol/l) throughout a 24-hour period by 37.6%, compared with control (additional 9 hours). The difference in time spent with target glycemia between closed-loop and control in nonhemodialysis patients of the main study[11] was 22.4%, indicating a trend toward a greater beneficial effect of the closed-loop system in the hemodialysis cohort. Hemodialysis patients in the control group spent less than one-third of the time in the target range, possibly due, at least in part, to fear of inducing hypoglycemia. A recent observational study in hospitalized dialysis patients with type 2 diabetes showed[6] that 1 in 5 (21.7%) individuals experienced glucose levels <3.0 mmol/l.

Guidelines for inpatient diabetes care suggest[14] the use of a basal-bolus insulin regimen. However, implementation can be challenged by high within- and between-day variation in insulin requirements. An outpatient study using euglycemic clamp methodology showed that insulin requirements are reduced by 25% up to 24 hours after hemodialysis.[7] Generalizability of this findings to an inpatient setting, however, may not be appropriate, especially in the context of variable daily dialysis schedules and concomitant acute illness.[15] Hence, a closed-loop system such as ours, which enables a

Table 1 | Primary and secondary endpoints during the entire study

Study endpoint	Closed-loop (n = 9)	Control (n = 8)	*P* value
Time spent at glucose level in mmol/l (%)			
5.6–10.0[a]	69.0 (12.0)	31.5 (13.5)	<0.001
>10	20.1 (9.8)	57.4 (25.7)	0.001
<5.6	10.9 (4.5)	11.1 (14.1)	0.96
<3.0	0.0 (0.0, 0.2)	0.0 (0.0, 0.6)	0.82
Mean glucose (mmol/l)	8.1 (0.6)	11.0 (2.3)	0.003
SD of glucose (mmol/l)	2.3 (0.5)	3.6 (1.2)	0.012
CV of glucose (%)	28.4 (4.9)	32.3 (8.5)	0.26
Between days CV of glucose (%)	13.4 (3.7)	21.8 (7.3)	0.008
AUC_{Day} <3.0 mmol/l (mg/dl × min)	0.0 (0.0, 2.1)	0.0 (0.0, 8.8)	0.89
Total daily insulin dose (U/24 h)	40.7 (25.7)	50.3 (20.6)	0.42

AUC_{Day}, area under the curve for a glucose concentration of <3.0 mmol/l per 24-hour period; CV, coefficient of variation.
[a]Primary endpoint.
Data are given as mean (SD), or median (interquartile range).

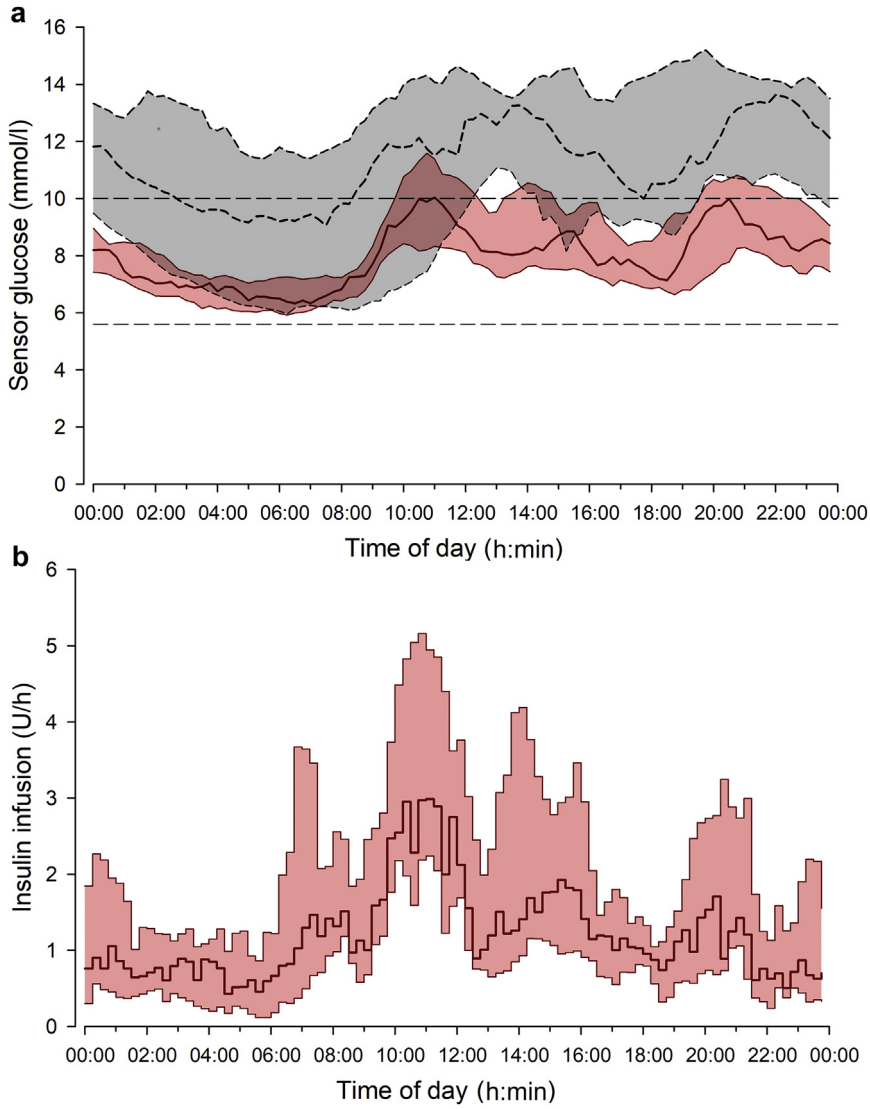

Figure 1 | Median (interquartile range) of sensor glucose during closed-loop (the solid red line and the red-shaded area) and control interventions (the dashed black line and the gray-shaded area) from midnight to midnight. The lower and upper limits of the glucose target range of 5.6–10.0 mmol/l are denoted by the horizontal dashed lines (**a**). Median (interquartile range) of algorithm-directed insulin delivery during closed-loop intervention (**b**).

finely tuned instantaneous glucose-responsive modulation of insulin delivery and continually adapts to changing insulin needs during the day and between days, may offer a more effective and safer diabetes therapy.

One strength of the current study is the random allocation of treatment and the identification of a new target group who may be particularly likely to benefit from a closed-loop system. However, in the absence of randomized outcome trials, the long-term clinical benefits of maintaining effective glycemic control in hemodialysis patients have yet to be established. Findings from observational studies are inconsistent. Although the study with the longest follow-up showed a clear association between high glycated hemoglobin and all-cause mortality,[16] this relationship was found to be either only in patients younger than 60 years[17] or without support.[18] In addition to the unclear accuracy of measures of glycated hemoglobin in dialysis patients,[19] assessments can be challenged by hypoglycemia, which is similarly associated with adverse events.[20] We acknowledge the limitation inherent in a subgroup analysis, such as small sample size and potential confounders that may limit the validity and generalizability of the results. However, our findings provide justification for evaluating further closed-loop insulin delivery use in inpatient and outpatient cohorts on maintenance dialysis.

CONCLUSION

Diabetes management in inpatients with type 2 diabetes undergoing hemodialysis is complex and often results in suboptimal glucose control. Fully automated closed-loop insulin delivery resulted in significantly better glycemic control than did conventional therapy, without increasing the risk of

hypoglycemia, thereby offering a novel treatment modality in this vulnerable population.

METHODS

Study design and participants

In a *post hoc* analysis of a randomized controlled trial, we compared fully automated closed-loop insulin delivery (n = 9) with conventional insulin therapy (n = 8) in hospitalized patients with type 2 diabetes undergoing hemodialysis for up to 15 days or until hospital discharge. Randomization was stratified according to glycated hemoglobin, body mass index, and total daily insulin dose.

The closed-loop group received a subcutaneous study pump (Dana R Diabecare, Sooil, Seoul, Republic of Korea) filled with rapid-acting insulin analogue (Humalog, Eli Lilly, Indianapolis, IN, or Novorapid, Novo Nordisk, Bagsvaerd, Denmark) coupled to a continuous glucose monitor (Freestyle Navigator II, Abbott Diabetes Care, Alameda, CA) by means of a model predictive control algorithm on a computer tablet (Dell Latitude 10 Tablet, Dell, TX). Glucose levels were controlled without announcement or bolusing for meals.

The control group received conventional subcutaneous insulin therapy according to local clinical practice, and continuous glucose monitoring was performed in a blinded mode.

The study did not interfere with or specify nutritional intake or any other clinical activities. Hemodialysis was carried out according to local clinical practice. Point-of-care capillary glucose measurements were performed as part of usual care by nursing ward staff in both groups.

Statistical analysis

Endpoints were analyzed according to intention-to-treat using unpaired *t*-tests or nonparametric equivalents for highly skewed variables. GStat software, Version 2.2 (University of Cambridge, Cambridge, UK) and SPSS, Version 21 (IBM Software, Hampshire, UK) were used for calculations. Values are reported as mean (SD) or median (quartile 1 to quartile 3). Two-tailed P values < 0.05 were considered statistically significant.

DISCLOSURE

SH serves as a consultant for Novo-Nordisk and for the ONSET group, and reports having received speaker/training honoraria from Medtronic (Minneapolis, MN). MLE reports having received speaker honoraria from Abbott Diabetes Care (Alameda, CA), Novo Nordisk (Bagsvaerd, Denmark), MSD, and Animas, serving on advisory panels for Novo Nordisk (Bagsvaerd, Denmark), Abbott Diabetes Care (Alameda, CA), Medtronic, Roche (Mannheim, Germany), Dexcom, and Cellnovo (Wales, UK). CS reports having received speaker honoraria from Medtronic and Ypsomed (Burgdorf, Switzerland), and serving on advisory panels for Novo Nordisk (Bagsvaerd, Denmark), Medtronic, Roche, and Sanofi (Paris, France). RH reports having received speaker honoraria from Eli Lilly (Indianapolis, IN) and Novo Nordisk (Bagsvaerd, Denmark), serving on advisory panels for Eli Lilly (Indianapolis, IN) and Novo Nordisk (Bagsvaerd, Denmark), and receiving license fees from BBraun and Medtronic. RH and MEW report patents and patent applications related to closed-loop insulin delivery. All the other authors declared no competing interests.

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