Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study

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Summary

Background **Closed-loop insulin delivery is a promising option to improve glycaemic control and reduce the risk of hypoglycaemia. We aimed to assess whether overnight home use of automated closed-loop insulin delivery would improve glucose control.**

Methods **We did this open-label, multicentre, randomised controlled, crossover study between Dec 1, 2012, and Dec 23, 2014, recruiting patients from three centres in the UK. Patients aged 18 years or older with type 1 diabetes were randomly assigned to receive 4 weeks of overnight closed-loop insulin delivery (using a model-predictive control algorithm to direct insulin delivery), then 4 weeks of insulin pump therapy (in which participants used real-time display of continuous glucose monitoring independent of their pumps as control), or vice versa. Allocation to initial treatment group was by computer-generated permuted block randomisation. Each treatment period was separated by a 3–4 week washout period. The primary outcome was time spent in the target glucose range of 3·9–8·0 mmol/L between 0000 h and 0700 h. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01440140.**

Findings **We randomly assigned 25 participants to initial treatment in either the closed-loop group or the control group, patients were later crossed over into the other group; one patient from the closed-loop group withdrew consent after randomisation, and data for 24 patients were analysed. Closed loop was used over a median of 8·3 h (IQR 6·0–9·6) on 555 (86%) of 644 nights. The proportion of time when overnight glucose was in target range was significantly higher during the closed-loop period compared to during the control period (mean difference between groups 13·5%, 95% CI 7·3–19·7; p=0·0002). We noted no severe hypoglycaemic episodes during the control period compared with two episodes during the closed-loop period; these episodes were not related to closed-loop algorithm instructions.**

Interpretation **Unsupervised overnight closed-loop insulin delivery at home is feasible and could improve glucose control in adults with type 1 diabetes.**

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See Comment page 679

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Introduction

Intensive insulin therapy has been the standard of care for management of type 1 diabetes since the Diabetes Control and Complications Trial.[1] However, tightening of glycaemic control increases the risk of hypoglycaemia,[2,3] which can be partly alleviated in adults by the use of modern insulin analogues[4] and educational interventions,[5] but such interventions fail in young people aged 11–16 years.[6] Individuals with type 1 diabetes continue to face daily challenges of complex insulin regimens involving many daily insulin boluses, frequent blood glucose monitoring, and unpredictable glucose excursions.[7] Advances in diabetes technology have emphasised their increasing role in clinical care. Continuous glucose monitoring devices measure interstitial glucose every 1–5 min, leading to improved glycaemic control.[8] Findings from randomised controlled trials have shown the benefits of sensor-augmented pump therapy in reducing HbA_{1c}.[9] The advent of the threshold-suspend feature allows insulin delivery to be suspended automatically for up to 2 h and can reduce the duration and frequency of hypoglycaemia.[10,11]

Closed-loop insulin delivery—ie, the artificial pancreas—is a novel approach that is more complex than, and differs from, conventional pump therapy and the threshold suspend approach. In a closed-loop system, a control algorithm autonomously increases and decreases subcutaneous insulin delivery on the basis of real-time sensor glucose concentrations, thereby mimicking physiological insulin delivery.[12] Findings from clinical research facility studies have shown that closed-loop insulin delivery is a feasible and safe option to improve glycaemic control and reduce the risk of hypoglycaemia.[13–15]

Findings from follow-up transitional and out-of-hospital single-night studies have been promising,[16,17] paving the way towards development of ambulatory closed-loop prototypes such as that used in a 3 week

single-centre study in adolescents.[18] We postulated that 4 week overnight unsupervised closed-loop insulin delivery at home in adults would improve glycaemic control without increasing the risk of hypoglycaemia.

Methods

Study design and participants

We did this open-label, multicentre, randomised, crossover study between Dec 1, 2012, and Dec 23, 2013, recruiting patients from three centres in the UK. We identified eligible adults from diabetes clinics who were attending Addenbrooke's Hospital (Cambridge, UK); Sheffield Teaching Hospitals (Sheffield, UK); and King's College Hospital (London, UK). Inclusion criteria were type 1 diabetes (WHO criteria), C-peptide negative, aged 18 years or older, insulin-pump therapy for at least 3 months, knowledge of insulin self-adjustment, undertaking of glucose self-monitoring at least four times daily, and HbA_{1c} of 10% (86 mmol/mol) or lower. Exclusion criteria were established nephropathy, neuropathy or proliferative retinopathy, total daily insulin dose of 2·0 U/kg or greater, regular use of continuous glucose monitoring within 1 month before enrolment, severe visual or hearing impairment, pregnancy, or breastfeeding.

Figure 1 shows the open-label, randomised controlled, crossover study design. After the run-in phase, participants applied insulin-pump therapy with real-time continuous glucose monitoring at home on two periods, with or without use of an overnight closed-loop system. Each period lasted 4 weeks. Identical study insulin pump and real-time continuous glucose monitoring device were used during the two study periods, which were separated by a 3–4 week washout, during which participants used their own pump and discontinued continuous glucose monitoring.

All participants provided written informed consent. The study protocol was approved by the East of England Central Cambridge Ethics Committee.

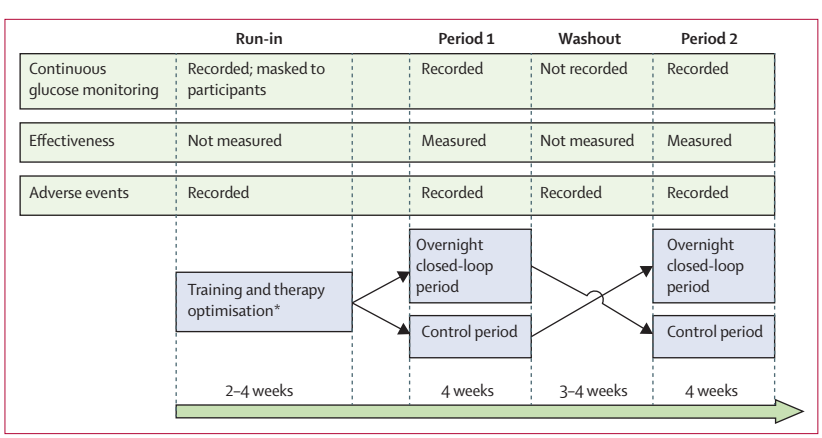

Figure 1: **Trial design**
*Compliance assessed.

Randomisation and masking

The order of the two study periods was randomly assigned following the run-in phase using computer generated permuted block randomisation. During run-in, the continuous glucose monitor receiver was modified and participants were masked to the recorded sensor glucose concentrations, and continued to monitor blood glucose with the built-in Freestyle Navigator capillary glucose meter (Abbott Diabetes Care, Alameda, CA, USA). Participants had access to sensor glucose readings after the end of the run-in phase. Investigators analysing study data were not masked to treatment allocation.

Procedures

On enrolment, participants were trained in how to use the study insulin pump (Dana R Diabecare, Sooil, Seoul, South Korea) and the FreeStyle Navigator device. Participants calibrated the real-time continuous glucose monitoring device according to manufacturer's instructions. During the run-in phase, we assessed compliance by assessing the number of days for which continuous glucose monitoring data were available from sensor glucose downloads. Each participant had to use the study pump and continuous glucose monitor for at least 2 weeks. At the end of the run-in phase, downloaded sensor glucose readings were used to optimise insulin-pump therapy. Participants used the rapid-acting insulin analogue normally used in their usual clinical care. Participants used the built-in bolus wizard of the insulin pump during both interventions to calculate insulin boluses at mealtimes and when administering correction boluses.

During the control period, participants used real-time continuous glucose monitoring and the study pump. The sensor glucose alarm threshold for hypoglycaemia was initially set at 3·5 mmol/L, but could be modified by the participants. During the closed-loop period, participants were admitted to the local clinical research facility for their first closed-loop night and received training in use of the closed-loop system, which was used under supervision overnight. Training lasted for 60–90 min and covered initiation and discontinuation of the closed-loop system, and problem troubleshooting. Participants were trained to do calibration checks before evening meals; if sensor glucose was greater than capillary glucose by more than 3 mmol/L, the continuous glucose monitor was recalibrated and the calibration check was repeated before starting the closed-loop system. These instructions reduced the risk of sensor error and the calibration check approach was effective when assessed by computer modelling.[19] If sensor glucose readings became unavailable, or in case of other system failures, participants were alerted by an audible alarm and the system restarted the participant's usual insulin delivery rate within 30–60 min to mitigate the risk of insulin underdelivery and overdelivery.[20]

From the second night onwards, participants used the closed-loop system unsupervised at home for 4 weeks.

Participants were instructed to start the system at home after their evening meal, and to discontinue it before breakfast the next morning. Participants were not restricted in dietary intake or daily activities. A 24-h telephone support service assisted participants in clinical or technical issues that arose during the study. All participants were given troubleshooting literature and user manuals for all study devices. Standard local hypoglycaemia and hyperglycaemia treatment guidelines were followed.

Blood samples for HbA_{1c}, fructosamine, random glucose, and C-peptide measurements were taken after enrolment. Additionally, we measured HbA_{1c} and fructosamine before and after each study period.

The Florence automated closed-loop system[21] comprised a model predictive control algorithm residing on a hand-held computer linked by cable to the continuous glucose monitoring receiver. Every 12 min, the treat-to-target algorithm calculated a new insulin infusion rate, which was automatically set on the study pump via wireless communication. The calculations used a compartment model of glucose kinetics[22] describing the effect of rapid-acting insulin and the carbohydrate content of meals on glucose concentrations. The algorithm was initialised with pre-programmed basal insulin delivery. At setup, on the first night during which the closed-loop system was used, the research team entered participants' weight and total daily insulin dose. Data for carbohydrate intake, as entered by participants into the insulin pump built-in bolus wizard, were automatically downloaded to the hand-held computer when the closed-loop system was turned on. Insulin delivery history, including manually instructed insulin boluses, was also automatically downloaded. The algorithm included rules that restricted maximum insulin infusion and suspended insulin delivery if glucose concentration was at or below 4·3 mmol/L or when it was rapidly decreasing. We used algorithm version 0.3.24 (University of Cambridge, UK).

We used a chemiluminescence immunoassay (Diasorin Liaison XL, Deutschland GmbH, Dietzenbach, Germany; interassay coefficients of variation 5·6% at 563 pmol/L, 4·5% at 2529 pmol/L, 5·8% at 5449 pmol/L) to measure baseline plasma C-peptide. We measured fructosamine with an enzymatic assay (Randox, Antrim, UK; interassay coefficients of variation 9·5% at 193 µmol/L, 6·4% at 430 µmol/L, 5·2% at 669 µmol/L). We measured HbA_{1c} centrally with ion exchange high-performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience, CA, USA; interassay coefficients of variation 1·3% at 31·2 mmol/mol, 0·8% at 80·5 mmol/mol).

Outcomes

The primary efficacy outcome was the time spent in the target glucose range (3·9–8·0 mmol/L) between 0000 h and 0700 h, as recorded by continuous glucose monitoring. Secondary outcomes included mean glucose concentration, time spent at concentrations lower than 3·9 mmol/L (hypoglycaemia) and greater than 8·0 mmol/L (hyperglycaemia), and insulin delivery. Overnight glucose variability was assessed by the SD and the coefficient of variation of continuous glucose monitoring levels. We assessed hypoglycaemia burden by calculation of the glucose sensor area under the curve less than 3·5 mmol/L and the number of nights with sensor glucose less than 3·5 mmol/L for at least 20 min. Outcomes were additionally calculated with adjusted sensor glucose with an assumption of a 15% measurement error to correct for bias resulting from simultaneous use of sensor glucose to direct insulin delivery.[23] We calculated secondary outcomes from 0000 h to 0700 h and over 24 h.

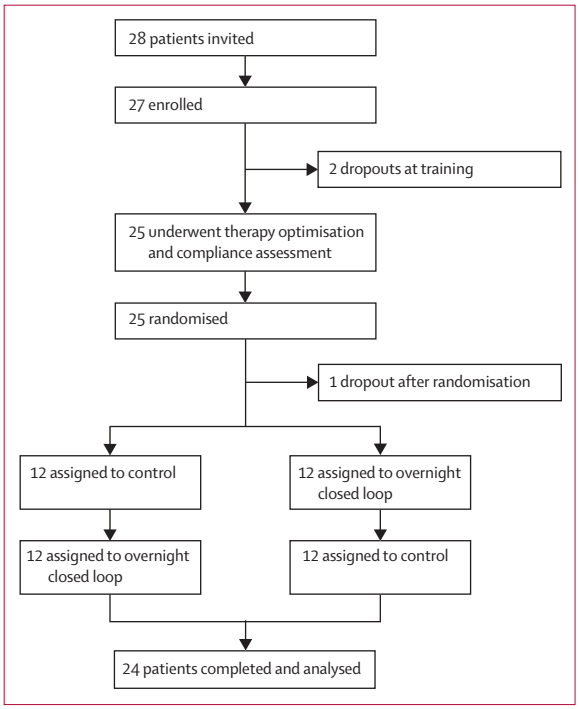

***Figure 2*: Trial profile**

	Data
Sex*	
Male	13 (54%)
Female	11 (46%)
Age (years)	43 (12)
BMI (kg/m^2)	26·0 (3·5)
HbA_{1c} (%)	8·1 (0·8)
HbA_{1c} (mmol/mol)	65 (9)
Duration of diabetes (years)	29 (11)
Time on pump (years)	6·3 (4·4)
Total daily insulin (U/kg per day)	0·5 (0·1)

Data are n (%) or mean (SD), unless otherwise indicated. *All C-peptide lower than 33 pmol/L.

***Table 1*: Baseline characteristics**

	Closed loop (n=24)	Control (n=24)	Paired difference* (n=24)	p value
Mean glucose (mmol/L)	8·2 (0·9)	9·0 (1·3)	–0·8 (1·3)	0·0052
SD of glucose (mmol/L)†	2·0 (0·3)	1·9 (0·3)	0·1 (0·4)	0·18
Within-night coefficient of variation of glucose (%)	24% (3)	21% (4)	3% (6)	0·010
Between-night coefficient of variation of glucose (%)	26% (6)	29% (7)	–3% (9)	0·11
Time spent at glucose concentration (%)				
3·9–8·0 mmol/L‡	52·6% (10·6)	39·1% (12·8)	13·5% (14·7)	0·0002
3·9–10·0 mmol/L	73·2% (9·0)	61·2% (13·7)	12·0% (14·2)	0·0004
>8·0 mmol/L	44·3% (11·9)	57·1% (15·6)	–12·8% (16·5)	0·0014
>16·7 mmol/L	1·1% (0·0 to 2·8)	1·5% (0·1 to 3·4)	–0·0% (–1·6 to 0·5)	0·54
<3·9 mmol/L	1·8% (0·6 to 3·6)	2·1% (0·7 to 3·9)	–0·3% (–2·4 to 1·0)	0·28
<3·5 mmol/L	0·7% (0·3 to 1·4)	0·7% (0·3 to 2·0)	0·3% (–17·4 to 3·4)	0·30
<2·8 mmol/L	0·2% (0·0 to 0·7)	0·2% (0·0 to 1·3)	0·0% (–0·9 to 0·2)	0·63
AUC less than 3·5mmol/L (mmol/L×min)§	4·0 (0·8 to 15·1)	5·3 (0·4 to 25·6)	0·3 (–17·4 to 3·8)	0·61
Number of nights when glucose <3·5 mmol/L¶	36 (5·4)	58 (8·6)	..	0·18
LBGI	0·67 (0·27 to 0·96)	0·62 (0·25 to 1·21)	–0·02 (–0·69 to 0·32)	0·44
Glucose at 2100 h (mmol/L)	8·6 (0·9)	9·3 (1·3)	–0·6 (1·3)	0·021
Glucose at 0000 h (mmol/L)	9·2 (1·3)	9·2 (1·7)	0·01 (1·2)	0·98
Glucose at 0700 h (mmol/L)	7·2 (0·9)	8·8 (1·2)	–1·6 (1·5)	<0·0001

Data are mean (SD) or median (IQR). AUC=area under the curve. LBGI=low blood-glucose index. *Closed loop minus control; positive value indicates measurement was higher on night of closed-loop delivery than with night of control. †Data in parentheses are the SD of SDs. ‡Primary endpoint. §AUC normalised per day. ¶Number of nights over 4 weeks when sensor glucose was <3·5 mmol/L for at least 20 min (total number of nights=644).

Table 2: **Comparison of overnight glucose control from 0000 to 0700 h during closed loop and control period with unadjusted (raw) sensor glucose over 28 days in the home setting**

We calculated differences in HbA_{1c} and plasma fructosamine concentrations to identify changes in metabolic control. We calculated outcomes with GStat software (version 2.0).

Statistical analysis

We based the power calculation on data from a previous study.[14] We postulated that overnight closed-loop insulin delivery would increase the proportion of night time for which glucose was between 3·9 mmol/L and 8·0 mmol/L by a mean of 13% (SD 25). We calculated that 24 participants would provide 80% power at the 5% significance level to detect a difference between sensor-augmented pump therapy and overnight closed-loop insulin delivery.

Analyses were done on an intention-to-treat basis. We compared normally distributed data with the paired *t* test and non-normally distributed data with Wilcoxon signed rank test. To assess end-period HbA_{1c}, a regression model adjusted for pre-period HbA_{1c} level was fitted to compare the two treatments. We did a similar analysis to assess changes in fructosamine. We report values as mean (SD) or median (IQR), unless stated otherwise. All p values are two-tailed. We did analyses with SPSS (version 21).

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Abbott Diabetes Care read the manuscript before submission. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 2 shows the trial profile. 25 eligible participants were randomised: nine (36%) from Addenbrooke's Hospital, eight (32%) from King's College Hospital, and eight (32%) from Sheffield. One participant from Sheffield withdrew consent after randomisation, meaning 24 participants completed the study and were analysed. Table 1 summarises baseline characteristics.

Table 2 shows results of the primary and secondary analyses. The time when overnight sensor glucose was in target range was higher during delivery of overnight closed-loop insulin (52·6% [SD 10·6]) than with control (39·1% [12·8])—a mean difference of 13·5% (95% CI 7·3–19·7; p=0·0002). No period (p=0·77) or carryover effect (p=0·84) was detected on the primary endpoint. Figure 3 shows sensor glucose profiles. In all but three participants, closed loop improved time spent in target range (figure 4). In one of those three participants, time spent in hypoglycaemia was reduced by 15·1% and in the other two by 2·4% and 2·7%. Closed loop reduced mean overnight glucose and time above target range without increasing time spent in the hypoglycaemia range. Time spent in hypoglycaemia at a glucose concentration of less than 3·9 mmol/L was low (median time less than

10 min per night) and similar during the two study interventions. We noted no significant differences in the burden of hypoglycaemia as measured by the area under the curve less than 3·5 mmol/L (p=0·61), number of nights during the study when sensor glucose was less than 3·5 mmol/L for at least 20 min (p=0·18), and the low blood glucose index[24] (p=0·44; table 2).

Increased time spent in target range and reduced mean overnight glucose (table 2, figure 4) was brought about by the closed-loop system delivering 30% more insulin than the control system overnight (table 3, figure 3); however, total daily insulin delivery did not differ between the two study interventions (table 3). Table 4 shows details from analysis of closed-loop operation. Closed-loop insulin delivery was unintentionally interrupted on average every 41 h (once every 5 nights). The most common cause of interruptions was the loss of wireless connectivity between handheld computer and insulin pump (table 4). The 24 h support line was contacted roughly four times per patient during each study intervention period (28 days; data not shown).

Overnight glucose variability was similar between the two interventions (table 2). The coefficient of variation of overnight glucose within each night was increased during the closed-loop period (table 2). Conversely, we recorded a trend towards a reduced between-nights coefficient of variation when patients were using the closed-loop system, accompanied by consistently reduced morning glucose (table 2). This trend was not associated with either increased time spent at glucose concentrations less than 3·9 mmol/L or area under the curve less than 3·5 mmol/L (appendix). Outcomes based on adjusted sensor glucose values were in concordance with those based on unadjusted sensor glucose; the proportion of time when adjusted overnight glucose was in target increased during closed-loop insulin delivery compared with control by a mean of 13·4% (SD 13·5; p=0·0001). Time above target was reduced by a mean of 11·9% (16·1; p=0·0014) and time below target was similar (2·2% [IQR 0·7–3·9] *vs* 2·5% [1·0–4·5]; p=0·21].

Table 5 shows endpoints calculated over a 24 h period from 0000 h to 0000 h. Overnight closed loop significantly reduced 24 h glucose by 0·5 mmol/L (p=0·0013) and increased proportion of time spent within wider target range (p=0·0016). Similar to the overnight period analyses, time when glucose was above 10·0 mmol/L was significantly reduced (table 5). Participants took an average of eight capillary glucose measurements per day. Overall sensor accuracy in relation to capillary glucose was good (median absolute deviation 0·8 mmol/L [IQR 0·3–1·5]; median absolute relative deviation 10·4% [4·7–19·3]). 78% of values were in Clarke Error Grid zone A. Median absolute relative deviation of sensor glucose during closed-loop and control interventions was 10·1% (IQR 4·5–18·7) and 10·7% (4·9–19·8), respectively.

The closed-loop intervention reduced mean HbA_{1c}, whereas no change was noted for control (before *vs* after closed loop: 7·9% [SD 0·8] *vs* 7·7% [0·8]; before *vs* after control: 7·9% [0·7] *vs* 7·9 [0·8]; p=0·033). Fructosamine was unchanged (460 [76] *vs* 454 [77]; 458 [98] *vs* 464 [84] µmol; p=0·75).

Two participants with history of hypoglycaemia unawareness each had an episode of severe hypoglycaemia during the closed-loop period (appendix). Both events happened at a time when the closed-loop system was not operational and one participant was receiving insulin delivery at the standard rate while the other was receiving insulin delivery at 50% of the standard rate. A post-hoc analysis identified that closed loop was interrupted about 1 hour before these events, because of disrupted wireless connectivity with insulin pump, and at the time when insulin delivery was suspended because of predicted low glucose concentrations. The events were not related to closed-loop algorithm instructions or performance of the closed-loop system. Although the cause of the episodes cannot

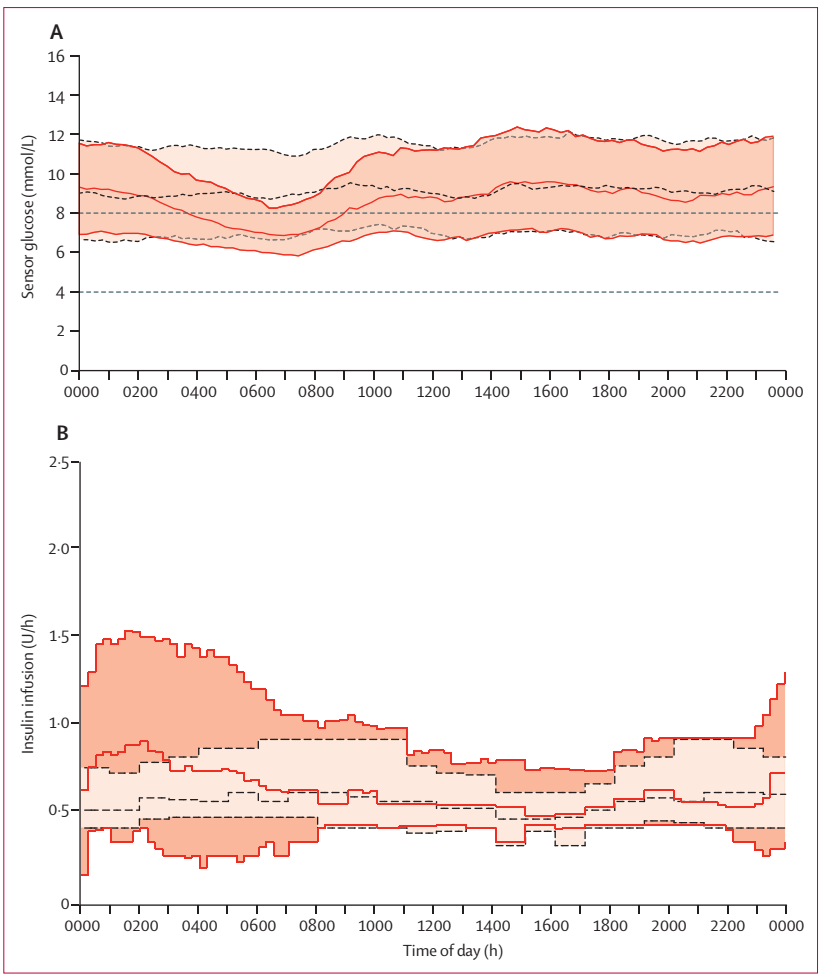

***Figure 3*: Median (IQR) of sensor glucose (A) and insulin delivery (B) during closed loop and control period for the 24 h duration**

Solid red line and red shaded area signify closed loop; dashed black line and peach shaded area signify control. The glucose range 3·9–8·0 mmol/L is denoted in panel A by horizontal black lines.

See Online for appendix

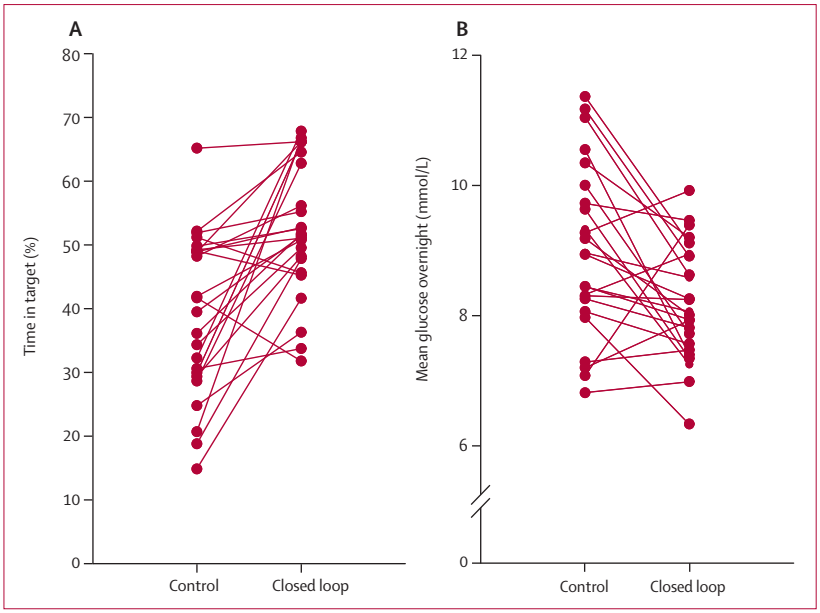

Figure 4: **Individual values of time when glucose was in target glucose range of 3·9–8·0 mmol/L (A) and mean overnight glucose (B)**

	Closed loop (n=24)	Control (n=24)	p value
Overnight insulin delivery (U)	6·4 (4·5–8·1)	4·9 (3·7–6·3)	0·0001
Total daily insulin delivery (U)	34·5 (29·3–48·4)	35·4 (29·7–45·2)	0·32
SD of overnight insulin delivery (U)*	0·6 (0·2)	0·1 (0·1)	<0·0001

Data are median (IQR) or mean (SD), unless otherwise indicated. *Data in parentheses are the SD of SDs.

Table 3: **Insulin delivery overnight (0000–0700 h) and over 24 h**

	Closed-loop operation
Number of nights when closed loop turned on	555/644 (86%)*
Time of day when closed loop turned on (h)†	2252 (2205–2344)
Time of day when closed loop turned off (h)†	0723 (0641–0829)
Duration of closed-loop operation at night (h)†	8·3 (6·0–9·6)
Total duration of closed-loop operation during the study (h)	4613
Number of events when closed loop interrupted (N=112)	
Lack of pump connectivity	68 (61%)
Unable to start closed-loop cycle within 30 min	21 (19%)
Unavailability of sensor data	7 (6%)
Temporary infusion changed by user	7 (6%)
Extended bolus changed by user	4 (4%)
Failure of handheld computer operating system	4 (4%)
Error in handheld computer software system	1 (1%)

*22 (92%) participants had 28 nights each; two (8%) participants had 14 nights each in accordance with advice from the Steering Committee advice to shorten their study period after events of severe hypoglycaemia. †Median (IQR) from all study nights when closed loop turned on.

Table 4: **Utility and failure analysis of closed-loop operation**

be known definitely, they were probably compounded by increased physical activity during the day in one participant, and a user error—resulting in overdelivery of insulin—whilst changing pump infusion rate when setting up the closed-loop system at night in the second participant. Both participants recovered fully with no clinical sequelae.

We recorded no other episodes of severe adverse events and no episodes of hyperglycaemia with ketosis. Four (17%) participants had mild to moderate respiratory tract infections during the closed-loop period, as did one (4%) participant during the control period. Two (8%) participants had episodes of viral gastroenteritis during the closed-loop period. One participant underwent an elective inguinal hernia repair during the washout period and continued the study after recovery.

Discussion

Our findings show the feasibility of 4 week home use of overnight closed-loop insulin delivery in adults. The closed-loop procedure improved glucose control, increasing the time spent in the target range and reducing mean glucose by delivering 30% more insulin overnight. Glucose concentrations remained lower in participants in the closed-loop group than in those in the control group throughout the daytime after closed loop was stopped, allowing participants to give less insulin bolus during breakfast and dinner periods. As such, the amount of total daily insulin during both interventions was similar. Time spent in hypoglycaemia was low, with few nights with glucose lower than 3·5 mmol/L during both interventions.

Achieving glycaemic concentration within the euglycaemic range, as safely as possible, presents a major challenge in patients with type 1 diabetes. The risk of hypoglycaemia is increased when glycaemic control is tightened.[25] Threshold-suspend pump therapy, which allows insulin delivery to be automatically suspended for up to 2 h when sensor glucose falls to lower than a preset threshold, represents the first step towards glucose-responsive insulin delivery. Studies in children and adults report reductions in the frequency and duration of nocturnal hypoglycaemia in individuals at greatest risk.[26,27] However, the threshold-suspend approach is not designed to step up insulin delivery and does not address the issue of overnight hyperglycaemia. After use of masked continuous glucose monitoring during the run-in period, participants used real-time sensor glucose during the control intervention to reduce time spent in hypoglycaemia, showing that the main driver for these individuals was hypoglycaemia avoidance. During the control intervention, glucose outcomes were similar between week 1 and week 4 suggesting rapid settling of glucose concentrations after start of real-time continuous glucose monitoring. Corrected-for-baseline HbA_{1c}, continuous glucose monitoring data obtained during the control intervention were similar to the Juvenile Diabetes Research Foundation continuous glucose monitoring trial;[8] the latter recruited adults with baseline HbA_{1c} of 7·6% who achieved a mean time of 68% with glucose

	Closed loop (n=24)	Control (n=24)	Paired difference* (n=24)	p value
Mean glucose (mmol/L)	8·7 (0·8)	9·3 (1·1)	−0·5 (0·7)	0·0013
SD of glucose (mmol/L)†	2·9 (0·4)	2·9 (0·4)	−0·0 (0·3)	0·79
Within-day coefficient of variation of glucose (%)	34·1% (31·1 to 35·8)	32·6% (30·0 to 34·1)	1·9% (−0·6 to 3·4)	0·016
Between-day coefficient of variation of glucose (%)	14·9% (12·4, 16·6)	15·3% (13·6 to 21·3)	..	0·11
Time spent at glucose level (%)				
3·9 to 10·0 mmol/L	66·0% (7·7)	59·7% (10·8)	6·4% (8·7)	0·0016
>10·0 mmol/L	30·8% (9·3)	37·3% (12·3)	−6·5% (8·7)	0·0013
>16·7 mmol/L	1·9% (1·0 to 2·9)	2·2% (1·0 to 3·0)	−0·6% (−1·2 to 0·5)	0·33
<3·9 mmol/L	1·7% (0·9 to 3·1)	1·7% (1·1 to 3·5)	−0·2% (-1·8 to 0·5)	0·27
<3·5 mmol/L	0·8% (0·4 to 1·4)	0·7% (0·5 to 1·6)	−0·2% (-0·8 to 0·3)	0·11
<2·8 mmol/L	0·2% (0·0 to 0·6)	0·2% (0·1 to 0·6)	0·0% (-0·3 to 0·2)	0·84
AUC less than 3·5 mmol/L (mmol/L×min)‡	4·7% (1·3 to 11·9)	4·5 (1·8 to 17·2)	−0·2 (−7·2 to 1·9)	0·42
LBGI	0·57% (0·36 to 0·84)	0·54 (0·34 to 0·96)	0·0 (−0·5 to 0·2)	0·57

Data are mean (SD) or median (IQR). AUC=area under the curve. LBGI=low blood-glucose index. *Closed loop minus control; positive value indicates measurement was higher during closed-loop intervention than with control. †Data in parentheses are the SD of SDs. ‡AUC normalised per day.

***Table 5*: 24 h glucose control during closed loop versus control with unadjusted (raw) sensor glucose over 28 days in the home setting**

concentrations in the target range between 3·9 mmol/L and 10·0 mmol/L over 24 h and 4·2% less than 3·9 mmol/L. The present study recruited adults with a slightly higher baseline HbA_{1c} of 8·1%, shown by a lower time in the target range of 60% and in the time spent in hypoglycaemia of 1·7%.

The advantage of a closed-loop system such as that in our study is the finely tuned modulation of insulin delivery both below and above the preset pump regimen. Day-to-day variations in insulin sensitivity are present in individuals with type 1 diabetes.[28] With information from participants' total daily insulin dose, basal insulin requirements, and sensor glucose values, our control algorithm could adapt and safely cope with variations in overnight insulin requirements, trading variability in insulin delivery for glucose consistency.

Early overnight closed-loop studies with our model predictive control algorithm in the research facility setting showed increased time spent in the target range and reduced time spent in hypoglycaemia.[14,29] Findings from a single-centre, 3-week, overnight, closed-loop study in the home setting showed improved glucose control and fewer nights with sensor glucose less than 3·5 mmol/L (10% *vs* 17% proportion of nights) in adolescents.[18] Before the present study, no other study had assessed the safety and effectiveness of unsupervised closed loop at home in adults for longer than 1 week (panel). We regarded a 4 week study intervention period as sufficient to provide useful experience with unsupervised overnight closed-loop home use by adults, and to allow progression to longer studies. Although nights with glucose concentrations less than 3·5 mmol/L were not significantly different, we recorded lower baseline hypoglycaemia than in previous studies,[16] with median time of less than 10 min spent at less than 3·9 mmol/L per night. Showing reductions in hypoglycaemia will be difficult to achieve without studying a larger or more hypoglycaemia-prone population.

The strength of our study is its multicentre design, which allowed us to assess a novel technology over a wider patient demographic showing generalisability. No restrictions were placed on participants' dietary intake or physical activity in the assessment of systems' performance during free living conditions. Previous trials showed improved glucose control with continuous glucose monitoring alone, particularly in regular users.[8] Our study was restricted by a duration of the control period that was too short to show a reduction in HbA_{1c}, as noted in previous trials of continuous glucose monitoring over 3 months or longer. Nevertheless, compliance with continuous glucose monitoring was high, with most participants using it regularly during this period. Regular use of hyperglycaemia threshold alarms and further increase in nocturnal insulin supplementation during the control period might have diminished the difference in mean glucose between the two interventions. However, this outcome might have resulted in additional hypoglycaemia during the control intervention, or reduced compliance of sensor glucose use due to alarm fatigue. Longer duration studies might provide additional information. We adopted a crossover design that had the benefit of each participant serving as their own control, and the possible confounding period or carry-over effects were not detected. The study was limited by disruptions of wireless connectivity and other reasons causing closed loop to be interrupted on average every 5 nights. Improved connectivity and reliability of follow-up prototypes might further increase usage to greater than in the present study, in excess of 85%.

In conclusion, unsupervised overnight closed loop at home is feasible and might improve glucose control in

Panel: Research in context

Systematic review

We searched PubMed for articles published up to Jan 24, 2014, with the search terms ("closed loop" OR "artificial pancreas") AND "type 1 diabetes", and identified four randomised controlled trials[16,18,30,31] of use of closed loop outside hospital settings. To date, no multicentre randomised control trial in adults at home has been done, with or without remote monitoring, or of a similar duration to the present study. A single-night study[16] at a diabetes youth camp with remote monitoring showed a reduction in the number of hypoglycaemic episodes with high baseline concentrations of hypoglycaemia; however, no significant improvement in the median glucose values overnight was reported. A 48 h home study[30] using a portable bi-hormonal closed-loop system, combining the delivery of insulin with subcutaneous glucagon, did not show any improvement in time spent within target range. Reduction of median glucose on day 2 of the closed-loop period was shown, but at the expense of a longer duration in the hypoglycaemic range. An interim analysis[31] of overnight closed loop over 4 nights at home showed improvements in hypoglycaemia endpoints, without improvement in the percentage of nights with normal mean glucose concentrations. The only unsupervised single-centre study[18] published was one of 3 week duration in adolescence. The reported benefits of overnight closed loop included increased time when glucose is in target, reduced mean glucose, and fewer nights with hypoglycaemia.

Interpretation

Our findings show an improvement in the time spent in target range and reduced glucose using a closed-loop insulin delivery system over 4 weeks in the home setting. These improvements were achieved by increasing insulin delivery overnight, but without changing the total daily insulin delivery or the time spent in hypoglycaemia. On the basis of these results, use of overnight closed loop at home for an extended period without remote monitoring or continuous supervision is feasible in adults with type 1 diabetes.

adults with type 1 diabetes. Longer term assessments are needed to strengthen the evidence of the benefits of overnight closed loop with use of systems with improved reliability.

Contributors

RH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RH coordinated the study. RH, MLE, SRH, SAA, DBD, KK, HT, EW, MEW, and KDB co-designed the studies. HT, AL-S, MS, LL, EW, AP, AI, and CN were responsible for screening and enrolment of participants and arranged informed consent from the participants. HT, AL-S, MS, LL, EW, AP, JMA, PC, AI, and CN provided patient care and/or took samples. MEW managed randomisation. HT, MN, LL, and MEW carried out or supported data analysis, including the statistical analyses. RH designed and implemented the glucose controller. HT, RH, MLE, SRH, SAA, AL-S, MS, LL, EW, AI, PC, KK, MEW, and DBD contributed to the interpretation of the results. All authors critically reviewed the report. No writing assistance was provided.

Declaration of interests

RH reports having received speaker honoraria from Minimed Medtronic, Lifescan, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Animas, Minimed Medtronic, and Eli Lilly, receiving licence fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun, Sanofi-Aventis, and Profil. SRH has undertaken consultancy for Novo Nordisk, Eli Lilly for which his institution has received payment. He has spoken at meetings for which he has received payment from NovoNordisk, Eli Lilly, Beckton Dickinson. Medtronic has provided research support for some of his work. MLE has received speaker honoraria from Eli Lilly, Animas, and Abbott Diabetes Care, and served on advisory panels for Medtronic, Roche, Sanofi-Aventis, and Cellnovo. PC declares speaker honoraria and travel support from Medtronic, Roche, and Lifescan, and has undertaken consultancy for Novo Nordisk, Eli Lilly for which his institution has received payment. He has spoken at meetings for which he has received payment from Novo Nordisk, Eli Lilly, and Beckton Dickinson. Medtronic has provided research support for some of his work. KK has spoken at meetings for which she received personal fees from Eli Lilly, Merck Sharpe & Dohme, and Sanofi. MEW reports receiving licensing fees from Beckton Dickinson. RH, DBD, and MEW report patent applications. HT, ALS, MS, LL, EW, AP, JMA, AI, MN, CN, KDB, and SAA declare no competing interests.

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