Home use of closed loop insulin delivery improves overnight glucose control in adults with type 1 diabetes: A four-week multicentre randomised crossover study

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Summary

Background—We assessed whether overnight home use of automated closed loop insulin delivery (artificial pancreas) improves glucose control.

Methods—We studied 24 adults with type 1 diabetes in a multicentre crossover study design comparing four weeks of overnight closed loop using a model predictive control algorithm to direct insulin delivery, with four weeks of insulin pump therapy in which participants used real-time display of continuous glucose monitoring independent of their pumps as control. Primary outcome was time when glucose was in the target range of 3·9 and 8·0mmol/l between midnight to 07:00. Analyses were by intention to treat. Trial registration ClinicalTrials.gov NCT01440140.

Findings—Closed loop was utilised over median 8·3 (interquartile range 6·0, 9·6)hours on 555nights (86%). Proportion of time when overnight glucose was in target range was significantly higher during closed loop compared to control by 13·5% (95% CI, 7·3–19·7; p<0·001). Mean overnight glucose (8·2±0·9 vs. 9·0±1·3mmol/l; p=0·005) and time spent above target (44·3%±11·9 vs. 57·1%±15·6; p=0·001) were significantly lower during closed loop. Time spent below target was low and comparable [1·8%(0·6, 3·6) vs. 2·1%(0·7, 3·9); p=0·28]. Lower mean overnight glucose was brought about by increased overnight insulin delivery [6·4 (4·5, 8·1) vs. 4·9 (3·7, 6·3)units; p<0·001] without changing the total daily insulin amount [34·5 (29·3, 48·4) vs. 35·4 (29·7, 45·2)units; p=0·32]. No severe hypoglycaemia episodes occurred during control period and two during closed loop not related to algorithm instructions.

Interpretation—Unsupervised overnight closed loop at home is feasible and may improve glucose control in adults with type 1 diabetes.

Introduction

Intensive insulin therapy has been the standard of care in the management of type 1 diabetes since the Diabetes Control and Complications Trial[1]. However, tightening glycaemic control increases the risk of hypoglycaemia[2,3], alleviated in part by modern insulin analogues[4] and educational interventions in adults[5] but not youth[6]. Individuals with type 1 diabetes continue to face daily challenges of complex insulin regimes involving multiple daily insulin boluses, frequent blood glucose monitoring, and unpredictable glucose excursions[7]. Recent advances in diabetes technology have highlighted their increasing role in clinical care. Continuous glucose monitoring devices measure interstitial glucose every one to five minutes leading to improved glycaemic control[8]. Randomised control trials demonstrated the benefits of sensor-augmented pump therapy in reducing HbA1c[9]. The advent of the threshold suspend feature allows insulin delivery to be suspended automatically for up to two hours and has been shown to reduce the duration and frequency of hypoglycaemia[10,11].

Closed loop insulin delivery, known as the artificial pancreas, is a novel approach which is more complex and differs from conventional pump therapy and the threshold suspend approach through a control algorithm that autonomously increases and decreases subcutaneous insulin delivery based on real-time sensor glucose levels thereby mimicking

physiological insulin delivery[12]. Clinical research facility studies have demonstrated closed loop insulin delivery to be a feasible and safe improving glycaemic control and reducing the risk of hypoglycaemia[13–15].

Follow-up transitional and 'out-of-hospital' single night studies have been promising[16,17] paving the way towards developing ambulatory closed loop prototypes such as that used in a three-week single centre study in adolescents[18]. In the present study, we hypothesised that four-week overnight unsupervised closed loop insulin delivery at home in adults may improve glycaemic control without increasing the risk of hypoglycaemia.

Methods

Participants and study design

We identified eligible adults from diabetes clinics attending Addenbrooke's Hospital, Cambridge, Sheffield Teaching Hospitals, Sheffield, and King's College Hospital, London. Inclusion criteria were type 1 diabetes (World Health Organisation criteria), C-peptide negative, age 18 years and older, insulin pump therapy for at least 3 months, knowledge of insulin self-adjustment, performing glucose self-monitoring at least four times daily, and HbA1c 10% (86mmol/mol). Exclusion criteria included established nephropathy, neuropathy or proliferative retinopathy, total daily insulin dose 2·0U/kg, regular use of continuous glucose monitoring within one month prior to enrolment, severe visual or hearing impairment, pregnancy or breast feeding. All participants signed informed consent prior to the start of study-related procedures. The study protocol was approved by the East of England Central Cambridge Ethics Committee.

Figure 1 outlines the open label randomised controlled cross-over study design. Following the run-in phase, participants applied insulin pump therapy with real-time continuous glucose monitoring at home on two periods with or without overnight closed loop. Each period lasted four weeks, Identical study insulin pump and real-time continuous glucose monitoring device were used during the two study periods, which were separated by a three to four-week washout during which participants used their own pump and discontinued continuous glucose monitoring.

Randomisation and masking

The order of the two study periods was random and was determined following the run-in phase using computer generated permuted block randomisation. During the run-in phase, the continuous glucose monitor receiver was modified and participants were blinded to the recorded sensor glucose levels. Participants had access to sensor glucose readings after the end of the run-in phase.

Procedures

On enrolment, participants were trained on the study insulin pump (Dana R Diabecare, Sooil, Seoul, South Korea) and continuous glucose monitoring device (FreeStyle Navigator, Abbott Diabetes Care, Alameda, CA, USA). 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 continuous glucose monitoring data were available from sensor glucose downloads. Each participant was required to use the study pump and continuous glucose monitor for at least two weeks. Downloaded sensor glucose readings at the end of the run-in phase were used to optimise insulin pump therapy. Participants used rapid acting insulin analogue normally used in their usual clinical care. The built-in bolus wizard of the study insulin pump was used by participants during both interventions to calculate insulin boluses at mealtimes and also when administering correction boluses.

During the control period, participants used real-time continuous glucose monitor and the study pump. The sensor glucose alarm threshold for hypoglycaemia was initially set at 3·5mmol/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 on the closed loop system which was used under supervision overnight. Training lasted 60 to 90minutes and covered initiation and discontinuation of the closed loop system as well as problem troubleshooting. Participants were trained to perform calibration checks before evening meal; if sensor glucose was above capillary glucose by more than 3mmol/l, the continuous glucose monitor was re-calibrated and calibration check was repeated before starting closed loop. 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 participant's usual insulin delivery rate within 30 to 60 minutes to mitigate the risk of insulin under- and over-delivery[20].

From the following night, participants used the closed loop system unsupervised at home for four weeks. Participants were instructed to initiate the system at home following their evening meal, and to discontinue it before breakfast the next morning. Participants were not restricted in dietary intake or daily activities. A 24-hour telephone support assisted participants in clinical or technical issues that arose during the study. Standard local hypoglycaemia and hyperglycaemia treatment guidelines were followed.

Blood samples for HbA1c, fructosamine, random glucose and C-peptide measurements were taken after enrolment. HbA1c and fructosamine were additionally measured before and after each study period.

Closed loop control algorithm

The Florence automated closed loop system[21] comprised a model predictive control (MPC) algorithm residing on a handheld computer linked by cable to the continuous glucose monitoring receiver. Every 12 minutes, the treat-to-target algorithm calculated a new insulin infusion rate, which was automatically set on the study pump using wireless communication. The calculations utilised a compartment model of glucose kinetics[22] describing the effect of rapid-acting insulin and the carbohydrate content of meals on glucose levels. The algorithm was initialised using pre-programmed basal insulin delivery. Participant's weight and total daily insulin dose were entered at setup by the research team on the first night of closed loop. Carbohydrate intake data entered by participants into the insulin pump built-in bolus wizard was automatically downloaded to the handheld computer when closed loop was

turned on. Insulin delivery history, including manually instructed insulin boluses, was also automatically downloaded. The algorithm included rules that limited maximum insulin infusion and suspended insulin delivery if glucose was at or below 4·3mmol/l or when glucose was rapidly decreasing. Algorithm version 0·3·24 was used (University of Cambridge).

Assays

We used a chemiluminescence immunoassay (Diasorin Liaison XL, Deutschland GmbH, Dietzenbach, Germany; inter-assay CV 5·6% at 563pmol/l, 4·5% at 2529pmol/l, 5·8% at 5449pmol/l) to measure baseline plasma C-peptide. We determined fructosamine using an enzymatic assay (Randox, Antrim, United Kingdom; interassay CVs 9·5% at 193 μmol/l, 6·4% at 430μmol/l, 5·2% at 669μmol/l). HbA1c was measured centrally using ion exchange high performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience Inc., CA, US; interassay CVs 1·3% at 31·2 mmol/mol, 0·8% at 80·5mmol/mol).

Sample size

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

Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance. The analyses were performed on an intention to treat basis. Each night was analysed to the treatment group assigned. The primary efficacy outcome was the time spent in the target glucose range (3·9 to 8·0mmol/l) between midnight and 07:00 as recorded by CGM. Secondary outcomes included mean glucose, time spent below 3·9mmol/l (hypoglycaemia) and above 8·0mmol/l (hyperglycaemia), and insulin delivery. Glucose variability overnight was assessed by the standard deviation and the coefficient of variation of CGM levels. Hypoglycaemia burden was assessed by calculating the glucose sensor area under the curve less than 3·5mmol/l and the number of nights with sensor glucose less than 3·5mmol/l for at least 20minutes. Outcomes were additionally calculated using adjusted sensor glucose assuming a 15% measurement error to correct for bias resulting from simultaneous use of sensor glucose to direct insulin delivery[23]. Secondary outcomes were calculated from midnight to 07:00 and over the 24 hour period. Differences in HbA1c and plasma fructosamine levels were calculated to determine changes in metabolic control.

Outcomes were calculated using GStat software, Version 2·0 (University of Cambridge, Cambridge, UK) and statistical analyses using SPSS, Version 21 (IBM Software, Hampshire, UK). Normally distributed data were compared using paired t-test while non-normally distributed data using Wilcoxon signed rank test. To assess end-period HbA1c, a regression model adjusted for pre-period HbA1c level was fitted to compare the two treatments. A similar analysis was carried out to assess changes in fructosamine. Values are

reported as mean±SD or median (quartile 1, quartile 3), unless stated otherwise. All p-values are two-tailed and values less than 0·05 were considered statistically significant.

Role of the funding and support sources

No sponsor had any 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 the publication.

Results

Twenty-seven participants were recruited from December 2012 to September 2013. Figure 2 shows flow of participants through the study. Two participants withdrew during the run-in phase. Twenty-five eligible participants were randomised; nine from Addenbrooke's Hospital Cambridge, eight from King's College Hospital London, and eight from Sheffield. One participant withdrew consent following randomisation. Data from 24 participants completing the study were analysed. Table 1 summarises baseline characteristics.

Primary and secondary analyses are shown in Table 2. The time when overnight sensor glucose was in target range, was significantly increased by a mean 13·5% (95% CI, 7·3–19·7, $p<0·001$) during overnight closed loop insulin delivery. No period ($p=0·77$) or carry-over effect ($p=0·84$) on primary endpoint was detected. Sensor glucose profiles are shown in Figure 3. In all but three participants, closed loop improved time spent in target range (Figure 4). In one of the 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 below 3·9mmol/l was low (median time less than 10 minutes per night) and comparable during the two study periods. There were no significant differences in the burden of hypoglycaemia as measured by the AUC below 3·5 mmol/l ($p=0·61$), number of nights during the study when sensor glucose was less than 3·5mmol/l for at least 20minutes ($p=0·18$) and the low blood glucose index[24] ($p=0·44$).

Increased time spent in target range and reduced mean overnight glucose (Table 2 and Figure 4) was brought about by closed loop delivering 30% more insulin overnight (Table 3 and Figure 3, bottom panel) but total daily insulin delivery did not differ between the two study interventions (Table 3). Overnight closed loop was utilised on 555 nights (86%); turned on at 22:52 (22:05, 23:44) and turned off at 07:23 (06:41, 08:29) operating over 8·3 (6·0, 9·6) hours (Table 4). Closed loop was unintentionally interrupted on average every 41 hours (once every 5 nights). The commonest cause (over 60%) of interruptions was the loss of wireless connectivity between handheld computer and insulin pump (Table 4). Other causes included inability to initiate closed loop cycle within 30 minutes, glucose sensor unavailability, and change of temporary infusion by user. Participants contacted the 24 hour support line approximately four times during the closed loop period.

Overnight glucose variability measured as the standard deviation was comparable during the two interventions. The coefficient of variation of overnight glucose within each night was

increased during closed loop. Conversely, a trend towards a reduced between-nights coefficient of variation was observed during closed loop, accompanied by consistently lower morning glucose (Table 2). This was not associated with increased time spent below 3·9mmol/l or AUC below 3·5mmol/l (Supplementary material, Table S1). Outcomes based on adjusted sensor glucose values were in concordance with outcomes based on unadjusted sensor glucose; the proportion of time when adjusted overnight glucose was in target increased during closed loop compared to sensor-augmented therapy by a mean of 13·4% (p<0·001). Time above target was reduced by a mean of 11·9% (p=0·001) and time below target was comparable [2·2 (0·7, 3·9) vs. 2·5 (1·0, 4·5) %, p=0·21].

Endpoints calculated from midnight to midnight are shown in Table 5. Overnight closed loop significantly reduced 24-hour glucose by 0·5mmol/l (p<0·001) and increased proportion of time spent within wider target range (p=0·002). Similar to the overnight period analyses, time when glucose was above 10·0mmol/l was significantly reduced. Participants performed on average eight capillary glucose measurements per day. Overall sensor accuracy in relation to capillary glucose was good with the median absolute deviation 0·8 (0·3, 1·5)mmol/l and the median absolute relative deviation of 10·4% (4·7, 19·3). Seventy-eight percent 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% and 10·7%, respectively.

Closed loop reduced HbA1c whilst no change was observed during control (7·9%±0·8 vs. 7·7%±0·8, pre- vs. post-closed loop; 7·9%±0·7 vs. 7·9%±0·8, pre- vs. post-control; p=0·033). Fructosamine was unchanged (460±76 vs. 454±77; 458±98 vs. 464±84µmol; p=0·754).

Two participants with history of hypoglycaemia unawareness each had an episode of severe hypoglycaemia during the closed loop period (Supplementary material, Figure S1 and S2). Both events occurred at a time when closed loop was not operational and one subject was receiving standard while the other 50% of standard insulin pump therapy insulin rate. A post-hoc analysis identified that closed loop was interrupted about an hour prior to these events due to lack of wireless connectivity with insulin pump and at the time when insulin delivery was suspended due to predicted low glucose levels. The events were not attributable to control algorithm insulin advice and, whilst it is not possible to know the cause of the episodes definitely, they were likely compounded by increased physical activity during the day in one participant, and a user-error resulting in over-delivery of insulin whilst changing pump infusion set at night in the second participant. Both participants recovered fully without any clinical sequelae.

No other episodes of severe adverse events and no episodes of hyperglycaemia with ketosis were reported. Four participants had mild to moderate respiratory tract infections during the closed loop period and one during control period. Two participants had viral gastroenteritis episodes during the closed loop period. One participant underwent an elective inguinal hernia repair during the washout period and continued the study after recovery.

Discussion

We demonstrated the feasibility of four-week home use of overnight closed loop insulin delivery in adults. Glucose control improved including increased time spent in the target range and reduced mean glucose by delivering 30% more insulin overnight. During closed loop intervention, glucose levels remained lower compared to control throughout the day-time after closed loop was stopped (Supplementary material, Table S2), allowing participants to give less insulin bolus during breakfast and dinner periods (Supplementary material, Table S3). As a result, total daily insulin amount during both interventions were comparable. Time spent in hypoglycaemia was low with few nights with glucose below 3·5mmol/l during both interventions.

Achieving glycaemic level within the euglycaemic range, as safely as possible, presents a major challenge in 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 two hours when sensor glucose falls below 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 those at greatest risk[26,27]. However, the threshold suspend approach is not designed to step up insulin delivery and does not address the problem of overnight hyperglycaemia. Following the use of masked continuous glucose monitoring during the run-in period, participants utilised real-time sensor glucose during the control intervention to reduce time spent in hypoglycaemia demonstrating that the primary driver for these subjects was hypoglycaemia avoidance (Supplementary material, Tables S4 and S5). During control intervention, glucose outcomes were similar between Week 1 and Week 4 indicating rapid settling of glucose levels once real-time continuous glucose monitoring was initiated (Supplementary material, Table S6). Corrected for baseline HbA1c, continuous glucose monitoring data collected during control intervention were comparable to the JDRF continuous glucose monitoring trial[8]; the latter recruited adults with baseline HbA1c of 7·6% achieving mean glucose levels of 68% in the target range between 3·9 and 10·0mmol/l over 24 hours and 4·2% below 3·9mmol/l. The present study recruited adults with a slightly higher baseline HbA1c of 8·1% reflected by a lower time in the target range of 60% and a lower time spent in hypoglycaemia of 1·7%.

The advantage of a closed loop system such as ours is the finely tuned modulation of insulin delivery below *and* above the preset pump regimen. Day-to-day variations in insulin sensitivity are present in individuals with type 1 diabetes[28]. Using information from participant's total daily insulin dose, basal insulin requirements and sensor glucose values, our control algorithm was able to adapt and safely cope with variations in overnight insulin requirements trading variability in insulin delivery for glucose consistency (Figure 3).

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]. A single centre three-week overnight closed loop study in the home setting demonstrated improved glucose control and fewer nights with sensor glucose below 3·5mmol/l (10% vs. 17%) in adolescents[18]. Prior to the present study, no other study

had been conducted assessing the safety and efficacy of unsupervised closed loop at home in adults for a period longer than one week. A four week study intervention period was considered 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 level below 3·5mmol/l were not significantly different, we observed lower baseline hypoglycaemia compared to previous studies[16] with median time of less than 10 minutes spent below 3·9mmol/l per night. Demonstrating 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, allowing the assessment of a novel technology over a wider patient demographic demonstrating generalizability. No restrictions were placed on participants' dietary intake or physical activity assessing system's performance during free living conditions. Previous trials demonstrated improved glucose control with continuous glucose monitoring alone particularly in regular users[8]. Our study was limited by a duration of the control period which was too short to demonstrate a fall in HbA1c observed in previous trials of continuous glucose monitoring over three 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 might have resulted in more hypoglycaemia during the control intervention, or reduced sensor glucose use compliance due to alarm fatigue. Longer duration studies may provide additional information. We adopted cross-over design which had the benefit of each subject serving as its 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 five nights. Improved connectivity and reliability of follow up prototypes may further increase usage above the present in excess of 85%.

In conclusion, unsupervised overnight closed loop at home is feasible and may improve glucose control in adults with type 1 diabetes. Longer term assessments are needed to strengthen the evidence of overnight closed loop benefits using systems with improved reliability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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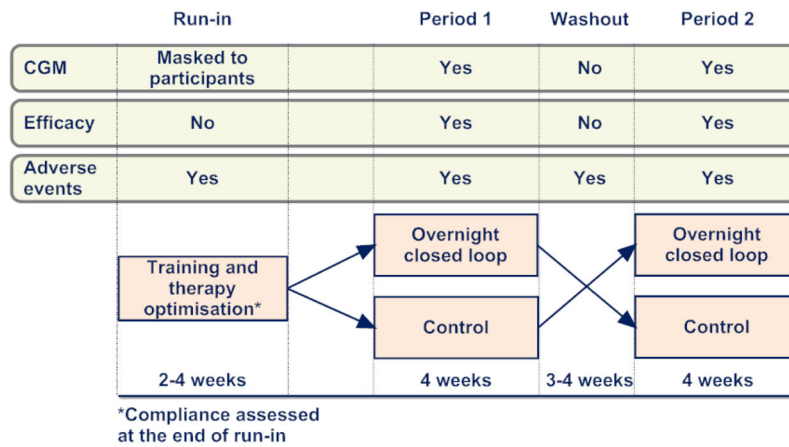
Figure 1.
Study design comparing overnight closed loop insulin delivery with control. The outline shows when continuous glucose monitoring data were collected, efficacy assessed, and adverse events monitored.
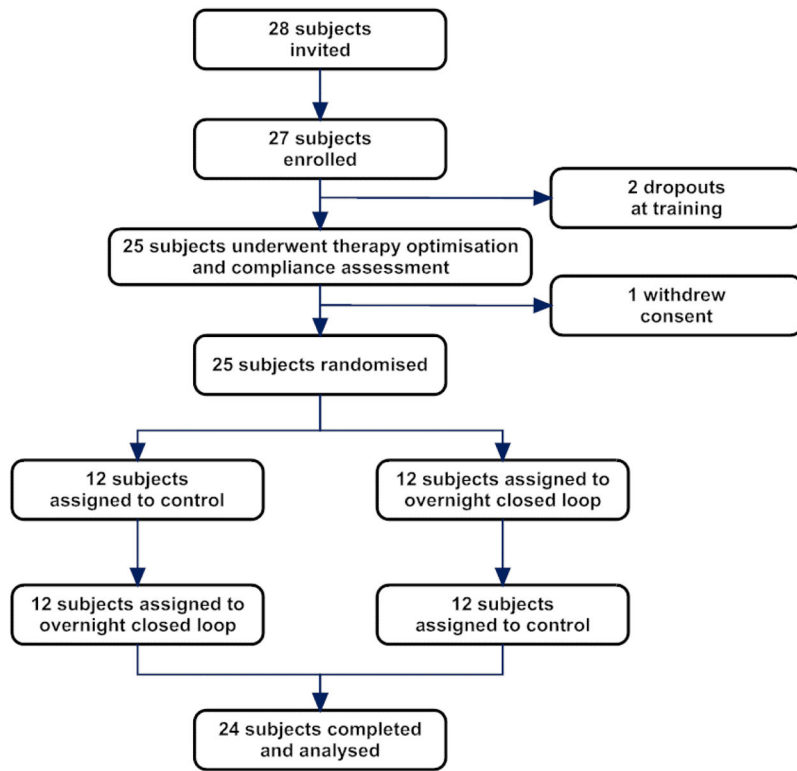
Figure 2.
Flow of participants through the trial.
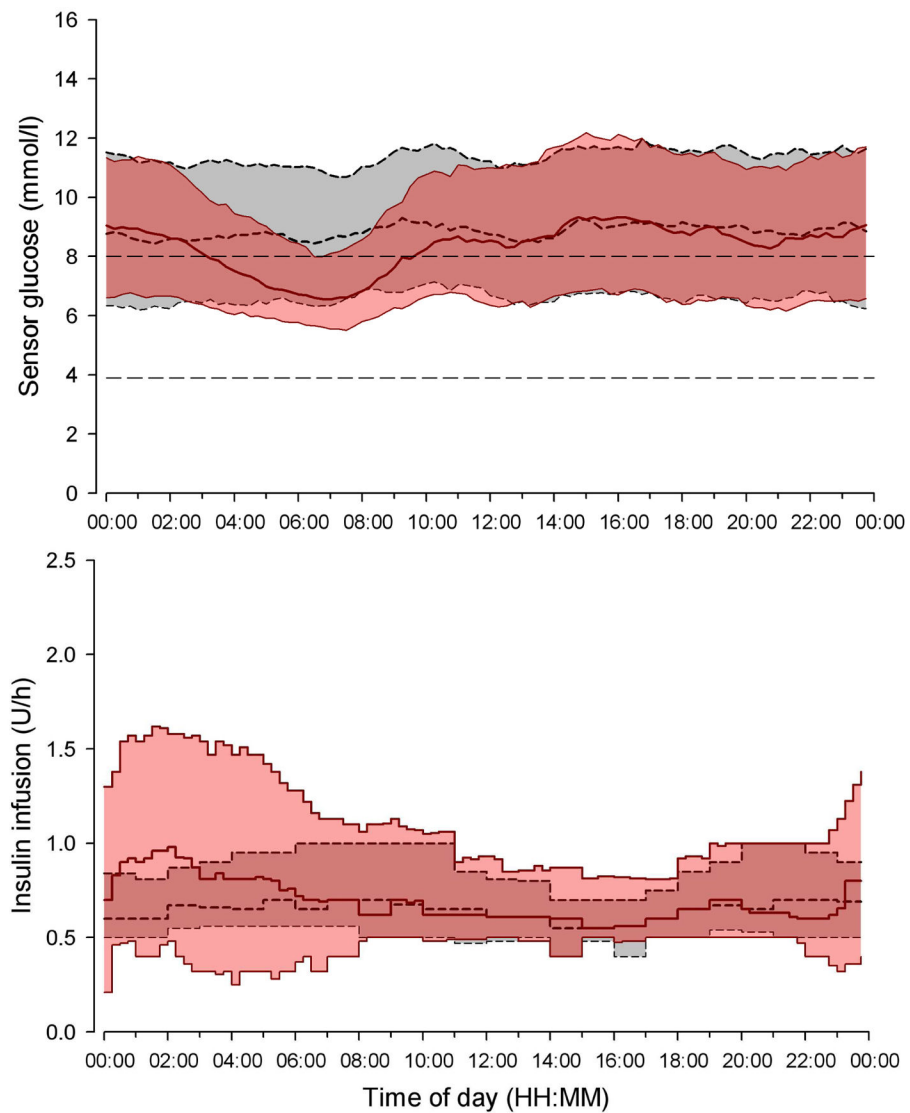
Figure 3.
Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during closed loop (solid red line and red shaded area) and control (dashed black line and gray shaded area) period for the 24-hour duration. The glucose range 3·9 to 8·0 mmol/l is denoted in the top panel by horizontal dashed lines.
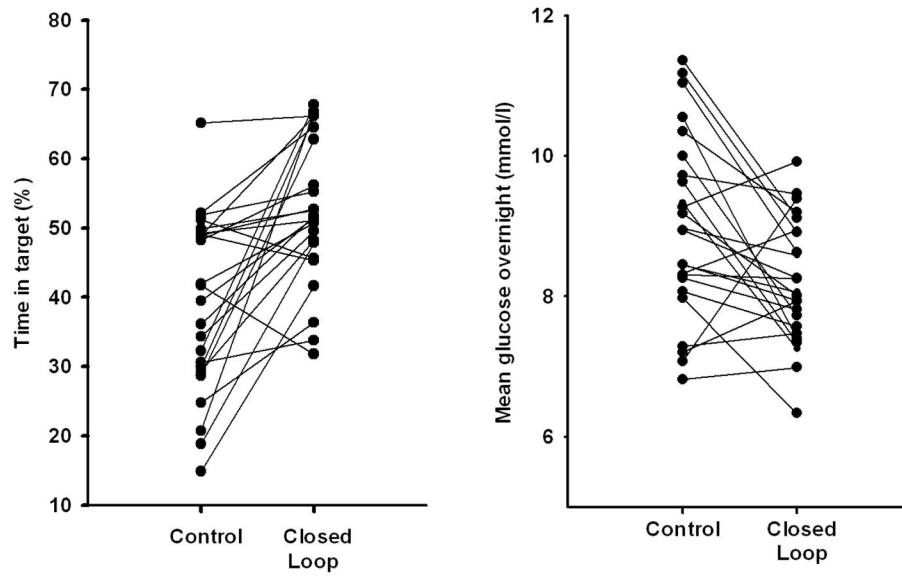
Figure 4.
Individual values of time when glucose was in target glucose range from 3·9 to 8·0 mmol/l (left panel) and mean overnight glucose (right panel) (n=24).

Table 1

Baseline characteristics (n = 24).

Gender (M/F)	13/11[*]
Age (years)	43±12
BMI (kg/m^2)	26·0±3·5
HbA1c (%)	8·1±0·8
HbA1c (mmol/mol)	65±9
Duration of diabetes (years)	29±11
Duration on pump (years)	6·3±4·4
Total daily insulin (U/kg/day)	0·5±0·1

[*] All C-peptide < 33pmol/l

Table 2

Comparison of overnight glucose control from midnight to 07:00 during closed loop and control period using unadjusted (raw) sensor glucose over 28 days in the home setting.

	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	0·005
SD of glucose (mmol/l)	2·0±0·3	1·9±0·3	0·1±0·4	0·18
Within night CV of glucose (%)	24±3	21±4	3±6	0·01
Between nights CV of glucose (%)	26±6	29±7	−3±9	0·11
Time spent at glucose level (%)				
3·9 to 8·0mmol/l[†],	52·6±10·6	39·1±12·8	13·5±14·7	<0·001
3·9 to 10·0mmol/l	73·2±9·0	61·2±13·7	12·0±14·2	<0·001
> 8·0mmol/l	44·3±11·9	57·1±15·6	−12·8±16·5	0·001
> 16·7mmol/l**	1·1 (0·0, 2·8)	1·5 (0·1, 3·4)	−0·0(−1·6, 0·5)	0·54
< 3·9mmol/l**	1·8 (0·6, 3·6)	2·1 (0·7, 3·9)	−0·3 (−2·4, 1·0)	0·28
< 3·5 mmol/l**	0·7 (0·3, 1·4)	0·7 (0·3, 2·0)	0·3 (−17·4, 3·4)	0·3
< 2·8mmol/l**	0·2 (0·0, 0·7)	0·2 (0·0, 1·3)	0·0 (−0·9, 0·2)	0·63
AUC$_{Day}$ below 3·5mmol/l** (mmol/l × minutes)	4·0 (0·8, 15·1)	5·3 (0·4, 25·6)	0·3 (−17·4, 3·8)	0·61
Number of nights when glucose <3·5mmol/l[‡]	36 (5·4%)	58 (8·6%)	-	0·18
LBGI**	0·67 (0·27, 0·96)	0·62 (0·25, 1·21)	−0·02 (−0·69, 0·32)	0·44
Glucose at 21:00 (mmol/l)	8·6±0·9	9·3±1·3	−0·6±1·3	0·02
Glucose at midnight (mmol/l)	9·2±1·3	9·2±1·7	0·01±1·2	0·9
Glucose at 07:00 (mmol/l)	7·2±0·9	8·8±1·2	−1·6±1·5	<0·001

[*] Closed loop minus control. Positive value indicates measurement was higher on night of closed loop delivery compared with night of control

Data are presented as mean ± SD, or **median (interquartile range)

[†] Primary endpoint

[‡] Number of nights over four weeks when sensor glucose was < 3·5mmol/l for at least 20 minutes.

LBGI = low blood glucose index; CGM = continuous glucose monitoring

Table 3

Insulin delivery overnight (00:00 – 07:00) and over 24-hour period.

	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)	<0·001
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	<0·001

Data shown are mean ± SD, or *median (interquartile range)

Table 4

Utility and failure analysis of closed loop operation.

Number of nights when closed loop turned on	555 (86%)
Time of day when closed loop turned on[*]	22:52 (22:05, 23:44)
Time of day when closed loop turned off[*]	07:23 (06:41, 08:29)
Duration of closed loop operation (hours)[*]	8·3 (6·0, 9·6)
Total duration of closed loop operation (h)	4613
Number of events when closed loop interrupted (% of total interruptions)	
lack of pump connectivity	68 (61)
unable to start closed loop cycle within 30 mins	21 (20)
sensor data unavailability	7 (6)
Temporary infusion changed by user	7 (6)
extended bolus changed by user	4 (4)
handheld computer operating system failure	4 (4)
handheld computer software system error	1 (1)

[*] Median (interquartile range) from all study nights when closed loop turned on

Table 5

Comparison of 24-hour glucose control during closed loop and control using unadjusted (raw) sensor glucose over 28 days in the home setting.

	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	0·001
SD of glucose (mmol/l)	2·9±0·4	2·9±0·4	−0·0±0·3	0·79
Within day CV of glucose (%)**	34·1 (31·1, 35·8)	32·6 (30·0, 34·1)	1·9 (−0·6, 3·4)	0·02
Between day CV of glucose (%)**	14·9 (12·4, 16·6)	15·3 (13·6, 21·3)	--	0·11
Time spent at glucose level (%)				
3·9 to 10·0mmol/l	66·0±7·7	59·7±10·8	6·4±8·7	0·002
>10·0mmol/l	30·8±9·3	37·3±12·3	−6·5±8·7	0·001
> 16·7mmol/l**	1·9 (1·0, 2·9)	2·2 (1·0, 3·0)	−0·6 (−1·2, 0·5)	0·33
< 3·9mmol/l**	1·7 (0·9, 3·1)	1·7 (1·1, 3·5)	−0·2 (−1·8, 0·5)	0·27
< 3·5mmol/l**	0·8 (0·4, 1·4)	0·7 (0·5, 1·6)	−0·2 (−0·8, 0·3)	0·11
< 2·8mmol/l**	0·2 (0·0, 0·6)	0·2 (0·1, 0·6)	0·0 (−0·3, 0·2)	0·84
AUC$_{Day}$ below 3·5mmol/l (mmol/l × minutes)**	4·7 (1·3, 11·9)	4·5 (1·8, 17·2)	−0·2 (−7·2, 1·9)	0·42
LBGI**	0·57 (0·36, 0·84)	0·54 (0·34, 0·96)	0·0 (−0·5, 0·2)	0·57

[*] Closed loop minus control. Positive value indicates measurement was higher during closed loop delivery intervention compared with control

Data shown are mean ± SD, or **median (IQR)