Day-and-Night Hybrid Closed-Loop Insulin Delivery in Adolescents with Type 1 Diabetes: A Free-Living, Randomized Clinical Trial

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Abstract

Objective

To evaluate feasibility, safety and efficacy of day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes under free-living conditions without remote monitoring or supervision.

Research Design and Methods

In an open-label randomized free-living crossover study design, 12 adolescents on insulin pump therapy (age 15.4±2.6years; HbA1c 8.3±0.9%; duration of diabetes 8.2±3.4years; mean±SD) underwent two seven-day periods of sensor-augmented insulin pump therapy or hybrid closed-loop insulin delivery without supervision or remote monitoring. During closed-loop, a model predictive algorithm automatically directed insulin delivery between meals and overnight; prandial boluses were administered by participants using a bolus calculator.

Results

The proportion of time when sensor glucose was in the target range (3.9 to 10mmol/l) was increased during closed-loop compared to sensor-augmented pump therapy (72% vs. 53%, p<0.001; primary endpoint), mean glucose was lowered (8.7 vs. 10.1mmol/l, p=0.028), and time spent above target was reduced (p=0.005) without changing the total daily insulin amount (p=0.55). Time spent in the hypoglycemic range was low and comparable between interventions.

Conclusions

Unsupervised day-and-night hybrid closed-loop at home is feasible and safe in young people with type 1 diabetes. Compared to sensor-augmented insulin pump

therapy, closed-loop may improve glucose control without increasing the risk of hypoglycemia in adolescents with suboptimally controlled type 1 diabetes.

Childhood onset type 1 diabetes is associated with significant morbidity and reduced life expectancy resulting from dysglycemia-related acute and long-term complications (1; 2). Adolescence is a particularly vulnerable period for onset and priming of cardiovascular and renal complications (3; 4) while the majority of young people with type 1 diabetes do not meet treatment targets (5; 6).

Diabetes management in adolescence is complicated by psychological and physiological changes accompanying puberty (7). Apart from hypoglycemia (8), reduced compliance is a major obstacle to achieving tight glucose control (9). Diabetic ketoacidosis is more common (10; 11), omission of or delayed insulin boluses with meals or snacks is widespread (9; 12), and discontinuation of insulin pump therapy is highest among adolescents (13). Sensor-augmented insulin pump therapy (14) and threshold-suspend features may alleviate burden of hypoglycemia and improve outcomes (15; 16), but acceptance and use of continuous glucose monitoring systems is notably reduced amongst teenagers (14; 17).

The artificial pancreas or closed-loop systems differ from conventional pump therapy and threshold-suspend approaches through the use of a control algorithm that autonomously and continually increases and decreases subcutaneous insulin delivery based on real-time sensor glucose levels (18). Results from studies under controlled laboratory settings (19-23) and investigations of closed-loop in transitional outpatient settings, incorporating remote monitoring and supervision by research staff in hotels (24) or at diabetes camps (25; 26), have demonstrated improved glucose control and reduction of hypoglycemia (25-28). First at-home studies of three weeks to three months application of overnight close-loop have been performed in adolescents and adults (29-32). However, home studies of

unsupervised day-and-night closed-loop application have been restricted to adults only (32; 33). There has been no previous evaluation of unsupervised day-and-night closed-loop in free-living settings in adolescents aged 10 to 18 years.

Here, we present the results of a seven-day-long day-and-night closed-loop home trial in adolescents with type 1 diabetes under free-living conditions. We hypothesized that day-and-night use of hybrid closed-loop insulin delivery without remote monitoring is feasible, safe and could improve glycemic control compared to sensor-augmented pump therapy in this population.

RESEARCH DESIGN AND METHODS

Study management and regulatory approvals

Prior to study initialization, approval was sought and received from the local independent research ethics committee and the UK regulatory authority (Medicines & Health products Regulatory Agency). An independent Data Safety and Monitoring Board oversaw the study and was informed of all unanticipated adverse events that occurred during the study.

Participants

Study participants were recruited between August 2014 and October 2014 through the pediatric diabetes clinic at Addenbrooke's Hospital, Cambridge, UK. Key inclusion criteria were age 10-18 years, diagnosis of type 1 diabetes, treatment with insulin pump therapy for at least three months, willingness to perform at least four

fingerstick glucose measurements per day, and HbA1c ≤11% (97mmol/mol). Exclusion criteria included established nephropathy, neuropathy, or proliferative retinopathy, total daily insulin dose ≥2.0 U/kg or <10 U/day, concurrent illness or medications likely to interfere with interpretation of study results, significant hypoglycemia unawareness as judged by the clinical investigators, recurrent incidents of severe hypoglycemia as defined by International Society for Pediatric and Adolescent Diabetes guidelines during the previous six months, more than one episode of diabetic ketoacidosis within 12 months prior to enrolment, pregnancy and breast-feeding. Participants aged ≥16 years and parents or guardians of participants aged <16 years signed informed consent; written assent was obtained from minors.

Study design

The study adopted an open-label prospective single center randomized crossover design contrasting automated closed-loop insulin delivery and sensor-augmented pump therapy over seven days (Supplemental Figure S1). The study was performed under free-living home conditions without remote monitoring or supervision by research staff, and participants performed their usual daily living activities. The participants were free to consume any meals of their choice and no restrictions were imposed on travelling or moderate exercise. All participants had access to a 24-hour telephone helpline to contact the study team in the event of study-related issues.

Study procedures

Blood samples for baseline HbA1c and non-hypoglycemia C-peptide levels were taken at enrolment. At the start of the run-in phase, participants were trained on

the use of the study insulin pump (DANA Diabecare R; Sooil, Seoul, South Korea) and study real-time continuous glucose monitoring device (FreeStyle Navigator II; Abbott Diabetes Care, Alameda, CA). The study insulin pump was programmed with the participant's usual basal settings, usual insulin-to-carbohydrate ratios and correction factors and delivered rapid-acting insulin analog (insulin aAspart, Novo Nordisk, Bagsvaerd, Denmark; or insulin lisproHumalog, Eli Lilly, Indianapolis, US). Participants were advised to use the bolus calculator for all meals during the entire study. Ability and competency to use study devices was formally assessed and additional training was provided as required. Over a one to two week run-in phase, participants were required to use the study pump and collect at least five days worth of sensor glucose to pass the compliance assessment. Data obtained during run-in phase were utilized for therapy optimization as per usual clinical practice.

After the run-in period, participants underwent two seven day periods, in random order, during which glucose was controlled either by sensor-augmented insulin pump therapy or hybrid closed-loop insulin delivery. The two treatment interventions were separated by one to four week wash-out period during which the participants could continue using the study insulin pump applying their standard pump settings. Continuous glucose monitoring was discontinued during wash-out.

The participants had the same number of planned contacts with the study team during the two study periods and used the study pump and the study real-time continuous glucose monitoring device during both study periods.

Randomization assignment was unblinded, but allocation between treatment sequences was concealed to the study staff until after randomization, which occurred

the day prior to the first intervention. Random permuted blocks were used for treatment sequence allocation.

On the first day of the closed-loop period, a two to three hour training session was provided by the investigators at the clinical research facility, including initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, meal bolus procedure, and the use of study devices during exercise. Prandial boluses were advised to be delivered before the meals using the pump's standard bolus calculator. Competency on the use of closed-loop system was assessed prior to discharge. After the training session, participants continued the study intervention for the next seven days under free-living conditions in their home and school environment. Automated closed-loop insulin delivery was continued during exercise of mild to moderate intensity, and exercise was announced to the algorithm. Participants were advised to discontinue closed-loop and follow their usual insulin pump therapy for certain activities such as periods of strenuous exercise, diving or contact sports.

Participants were advised to calibrate the continuous glucose monitoring device according to the manufacturer's instructions, and use the built-in glucometer for all fingerstick measurements; they were free to decide on alarm thresholds for the continuous glucose monitoring device. Participants followed their standard clinic guidelines for hypoglycemia and hyperglycemia treatment.

Closed-loop system

The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK)(34) comprised a model predictive control algorithm (version 0.3.30, University of

Cambridge) residing on a smartphone (Nexus 4, LG, South Korea), which communicated wirelessly with continuous glucose monitoring receiver through a purpose made translator unit (Triteq, Hungerford, UK) (Supplemental Figure S2). Every 12 min, the control algorithm calculated a new insulin infusion rate which was automatically set on the study insulin pump. The calculations utilized a compartment model of glucose kinetics (35) describing the effect of rapid-acting insulin analogues and the carbohydrate content of meals on glucose levels. In this trial, a hybrid closed-loop approach was applied, in which participants additionally administered prandial insulin for all meals using the standard bolus calculator. The control algorithm was initialized using preprogrammed basal insulin doses downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the particular participant. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8mmol/l and 7.3mmol/l and adjusted the actual level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions. Though devices were advised to be kept in vicinity to each other, a wireless transmission range of several meters allowed for flexibility in terms of device wear, appropriate cases, clips and pouches were provided.

The continuous glucose monitoring receiver provided hypoglycemia and hyperglycemia alarms, the insulin pump provided standard alarms, and the smartphone alerted the user about aspects related to closed-loop operation such as when closed-loop started or stopped.

Safety precautions during closed-loop

Participants performed a calibration check before breakfast and the evening meal. If the sensor glucose was above the fingerstick glucose by >3.0mmol/l, the continuous glucose monitoring device was manually recalibrated. There was no recalibration for sensor under reading. These instructions resulted from an in silico evaluation of hypoglycemia and hyperglycemia risk (36) using the validated Cambridge simulator (37).

If sensor glucose became unavailable or in case of other failures, preprogrammed insulin delivery automatically restarted within 30-60 min. This limited the risk of insulin under- and over delivery (36). Safety rules limited maximum insulin infusion and suspended insulin delivery if glucose was ≤4.3 mmol/l or when sensor glucose was rapidly decreasing.

Assays

HbA1c was measured using ion exchange high performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience Inc., CA, US; interassay CVs 1.3% at 31.2mmol/mol, 0.8% at 80.5mmol/mol). C-peptide measurements were performed using chemiluminescence immunoassay (IV2-004; Invitron Ltd, Monmouth UK; inter-assay variation 7.8%, 4.3% and 6.7% at 268pmol/l, 990pmol/l and 1,862pmol/l, respectively). Analytical sensitivity for the C-peptide assay was 5pmol/l.

Study outcomes

The primary outcome was the proportion of time when glucose was in the target range (3.9-10.0mmol/l) during the seven day study periods. Secondary

outcomes included mean sensor glucose levels, glucose variability, and time spent below and above glucose target. Outcomes were calculated during day-and-night, daytime and overnight periods; daytime was classified between 08:00 and midnight, and nighttime between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycemia burden was assessed by calculating the glucose sensor area under the curve less than 3.5mmol/l.

Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance. All analyses were undertaken on an intention-to-treat basis. Efficacy and safety data from all randomized participants with or without protocol violation were included in the analyses. The respective values obtained during the seven day randomized interventions contrasting the closed-loop system against the sensor-augmented pump therapy were compared using a least-square regression model. Sensor glucose outcomes were adjusted for baseline glucose level and period effect; insulin outcomes for period effect. Rank normal transformation analyses were used for highly skewed endpoints. Outcomes were presented as mean ± SD for normally distributed values or as median (interquartile range) for non-normally distributed values. Secondary outcomes for daytime and nighttime periods were excluded from calculating p-values to limit multiple comparisons. Outcomes were calculated using GStat software (University of Cambridge, version 2.2). Analysis was done using SAS

(SAS Institute, USA, version 9.4). A 5% significance level was used to declare statistical significance. All p-values are two-sided.

RESULTS

Participants

Fourteen subjects were screened. Supplemental Figure S3 shows the flow of participants through the study. One participant did not meet the inclusion/exclusion criteria, and another voluntarily withdrew consent and did not complete the run-in phase. Twelve eligible participants were randomized, completed the study, and provided data for analyses (8 males; age 15.4±2.6 years; diabetes duration 8.2±3.4 years; HbA1c 8.3±0.9% [68±10mmol/mol]; insulin pump therapy duration 5.6±2.9years; total daily insulin dose 0.84±0.22 U/kg/day]) (Supplemental Table S1).

Day-and-night glucose control and insulin delivery

The primary endpoint, the proportion of time sensor glucose was in the target glucose range 3.9 to 10.0mmol/l, significantly increased during closed-loop ($p<0.001$, Table 1). Twenty-four hour sensor glucose and insulin delivery profiles are shown in Figure 1. Closed-loop significantly reduced the mean glucose ($p=0.028$) and time spent above target glucose level ($p=0.005$) without increasing time spent in hypoglycemia (Table 1 and Figure 2). Proportion of time when sensor glucose was in hypoglycemic range (below 3.9mmol/l and 2.8mmol/l) and the area under the curve when sensor glucose was less than 3.5mmol/l were low and comparable during the study periods.

There was no difference in glucose variability between study periods as measured by the standard deviation and coefficient of variation of sensor glucose. Increased time when glucose was in target range and reduced mean glucose was achieved by closed-loop through increased variability of basal insulin delivery but without increasing total daily insulin (p=0.55). Higher total basal insulin delivery during closed-loop (p=0.001) was offset by a trend towards lower bolus delivery (p=0.06) presumably due to lower glucose levels resulting in reduced correction boluses (Table 1).

Daytime and overnight glucose control and insulin delivery

Secondary outcomes calculated for daytime and overnight periods are shown in Supplemental Table S2. Daytime and overnight outcomes were similar to outcomes over day-and-night. Proportion of time when sensor glucose was in daytime target range (3.9 to 10.0mmol/l) and overnight target range (3.9 to 8.0mmol/l) tended to be higher during closed-loop compared to control [*daytime*: 66% (55% to 68%) vs. 49% (46% to 51%); *overnight*: 63% (49% to 78%) vs. 40% (30% to 48%)]. Daytime mean glucose (9.4±1.2mmol/l vs. 10.3±1.4mmol/l)~~]~~ and overnight mean glucose (7.8±1.8mmol/l vs. 9.7±1.8mmol/l)~~]~~ tended to be lower during closed-loop without a difference in total daytime and overnight insulin amount.

Adverse events

No serious adverse events or severe hypoglycemic episodes were observed during either study period. Two participants measured mild to moderate elevated blood ketones (>2.00mmol/l) associated with hyperglycemia, one participant during closed-loop and one participant in the control period. These events were attributed to infusion set failures and were all self-managed.

Utility analysis

Closed-loop was operational over 91% (75% to 96%)] of time. Availability of sensor glucose was 98% (93% to 100%)] during closed-loop and 97% (92% to 100%)] during control period. On average, closed-loop was interrupted 1.1 times (0.6 to 1.5)] per subject per day. Apart from two occasions requiring closed-loop system reset by research staff, the participants were able to resolve issues on their own, such as restarting closed-loop after loss of pump connectivity or sensor data unavailability.

CONCLUSIONS

To our knowledge, this is the first trial investigating day-and-night application of closed-loop insulin delivery under free-living conditions in adolescents with type 1 diabetes. Results of the present study demonstrate the feasibility of unsupervised free-living home use of 24/7 hybrid closed-loop in this challenging population. Closed-loop increased the time when glucose was in the target range while reducing the mean glucose. These improvements were achieved without increasing the risk of hypoglycemia and without increasing the total daily insulin dose.

The occurrence of hypoglycemia exposure in the present study was low. Compared with previously published day-and-night adult outpatient studies using single-hormone (32; 33) or dual-hormone approaches with glucagon co-administration (27), participants in the present study spent less time at glucose levels below 3.9mmol/l during control period. During the closed-loop study arm our results matched the findings observed in adults (Table 2). In our adolescent cohort, the 24/7 hybrid closed-loop system managed to keep time in hypoglycemia on a low level, while significant reductions in hypoglycemia risk using closed-loop in outpatient settings were seen in more hypoglycemia prone populations (27, 32, 33).

The advent of novel technologies such as threshold-suspend insulin pump therapy (15) and more recently predictive low glucose suspend (16) may reduce hypoglycemia risk. However, these approaches are not designed to increase insulin delivery and do not address the issue of hyperglycemia, which poses major challenges in diabetes management of adolescents. The important advantage of a closed-loop system is highly responsive graduated modulation of insulin delivery

both below and above the pre-set pump regimen, allowing for improvements in time spent with target glucose values and reduction of mean glucose without increased hypoglycemia.

Closed-loop use and sensor wear were high in our cohort. This may be attributed to the relatively short intervention period and motivational bias of study participants. These findings are in line with previous observations regarding overnight closed-loop home application over longer intervention periods in adolescents (31). In terms of psychosocial impact and acceptance, overnight closed-loop technology was well accepted in this age group, with overall benefits outweighing practical challenges such as technical difficulties, intrusiveness of alarms, and size of the devices (38). Given high closed-loop utilisation in adolescents, the positive perception of this technology and its benefits in terms of glycemic control demonstrated by the present study, closed-loop represents a promising tool to address glycemic deterioration ~~(7; 39) and reduced adherence~~ commonly seen in adolescence (7; 39) ~~(40)~~.

The strengths of our study include the integration of closed-loop into normal life including use at school, and during weekends and holidays. The study was performed without remote monitoring or close supervision. No restrictions were imposed on dietary intake, moderate physical activity or travel. The comparator was 'state-of-the-art' sensor-augmented insulin pump therapy. A crossover design had the benefit of each participant acting as his/her own control. Weaknesses include the small sample size, the~~and~~ relatively short study duration, and limited use of the closed-loop system during strenuous exercise. The current closed-loop prototype system requires participants to wear and carry multiple devices. Further integration

of devices may reduce this burden and enhance usability of closed-loop systems, particularly during physical activity. A more adaptive control algorithm might further enhance daytime benefits.

In conclusion, we have demonstrated that day-and-night hybrid closed-loop can be used safely in adolescents at home without supervision. Its benefits include increased time when glucose is in the target range and reduced mean glucose. Larger and longer studies are warranted.

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Author contributions: RH had full access to all of the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analysis. RH coordinated the studies. RH, DBD, CLA, MT, MEW and HT co-designed the studies. MT and JMA were responsible for screening and enrolment of participants, and arranged informed consent from the participants. MT, JMA, MEW, HT, and ZS provided patient care and/or took samples. MEW managed randomization. MT, MEW, RH, PC and CK carried out or supported data analysis, including the statistical analyses. RH designed and implemented the glucose controller. RH, DBD, CLA, MT, HT and ZS contributed to the interpretation of the results. All authors critically reviewed the report. MT and RH wrote the manuscript. No writing assistance was provided.

Conflict of interest disclosures: RH reports having received speaker honoraria from Minimed Medtronic, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Eli Lilly, receiving license fees from BBraun and Medtronic; and having served as a consultant to BBraun, Sanofi-Aventis, and Profil. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. RH, DBD and MEW report patent applications. MT, JMA, HT, ZS, PC, CK and CLA declare no competing financial interest exists.

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Role of funding source

Abbott Diabetes Care read the manuscript before submission. No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Table 1. Comparison of glucose control and insulin delivery during closed-loop and control period.

	Closed-loop (n=12)	*Control (n=12)*	*P-value*
Time spent at glucose level (%)			
3.9 to 10.0mmol/l*	72 (59 to 77)	53 (46 to 59)	<0.001
>10.0mmol/l	26 (21 to 35)	43 (38 to 52)	0.005
<3.9mmol/l	2.9 (1.8 to 4.8)	1.7 (0.9 to 5.1)	0.87
<2.8mmol/l	0.2 (0.0 to 0.6)	0.1 (0.0 to 0.6)	0.67
AUC_{day} <3.5mmol/l (mmol/l x min) †	6.4 (2.8 to 23.7)	4.3 (1.8 to 13.6)	0.77
Mean glucose (mmol/l)	8.7±1.1	10.1±1.3	0.028
Within day SD of glucose (mmol/l)	3.5 (3.3 to 4.2)	4.0 (3.6 to 4.6)	0.21
CV of glucose within day (%)	41 (40 to 45)	39 (38 to 44)	0.36
CV of glucose between days (%)	17 (11 to 22)	19 (17 to 25)	0.80
Total daily dose (U/day)	57.3 (45.6 to 65.2)	56.6 (44.7 to 61.3)	0.55
Total bolus (U/day)	31.9 (21.2 to 41.0)	38.3 (26.4 to 41.4)	0.06
Total basal (U/day)	24.3 (22.8 to 28.8)	20.3 (19.1 to 22.1)	0.001
CV of basal insulin (%)	94 (91 to 103)	16 (13 to 26)	<0.001

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

* Primary endpoint

† AUC_{day}, glucose area under curve below 3.5mmol/l per day

Table 2. Comparison of percentage of time spent below 3.9 mmol/l during day-and-night closed-loop studies in outpatient settings.

Study population	Settings	Sample size	Intervention period	Time spent at glucose level below 3.9mmol/l (%)		Reference
				Closed-loop	Control	
Adults*	mixed†	20	5 days	4.1±3.5	7.3±4.7	(27)
Adults‡	home	17	1 week	3.1±2.6	4.3±3.6	(33)
Adults‡	home	33	12 weeks	3.1±1.9	4.3±3.9	(32)
Adolescents‡	home	12	1 week	3.7±2.7	3.3±3.7	present study

Data are presented as mean±SD

* Dual-hormone closed-loop vs. usual care (45% of participants used real-time continuous glucose monitoring during usual care)

† Control: home; closed-loop: restricted geographical area during day & hotel overnight

‡ Single-hormone closed-loop vs. sensor-augmented pump therapy

Figure 1. 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 period (dashed black line and gray shaded area) from midnight to midnight. The glucose range 3.9 to 10.0 mmol/l is denoted by horizontal dashed lines (top panel).

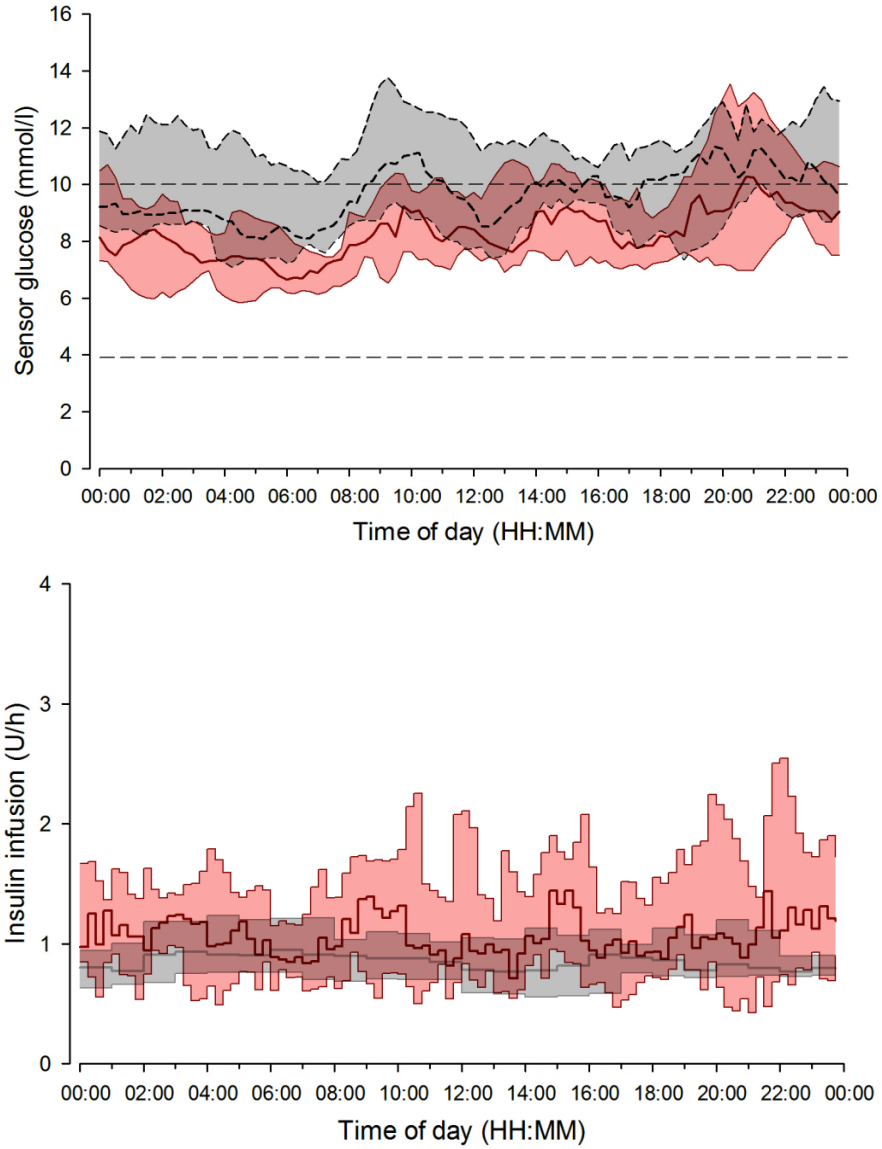
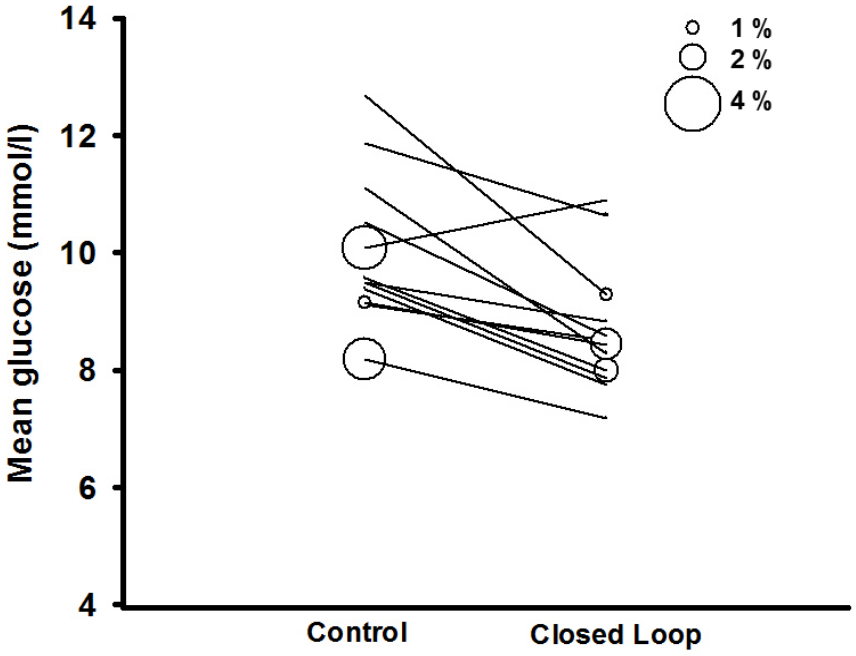


Figure 2. Individual values of mean sensor glucose during day-and-night closed-loop study. The size of bubble indicates the proportion of time spent with low glucose below 2.8mmol/l.



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