Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial

Hood Thabit, Sara Hartnell, Janet M Allen, Andrea Lake, Malgorzata E Wilinska, Yue Ruan, Mark L Evans, Anthony P Coll, Roman Hovorka

Summary

Background We assessed whether fully closed-loop insulin delivery (the so-called artificial pancreas) is safe and effective compared with standard subcutaneous insulin therapy in patients with type 2 diabetes in the general ward.

Methods For this single-centre, open-label, parallel-group, randomised controlled trial, we enrolled patients aged 18 years or older with type 2 diabetes who were receiving insulin therapy. Patients were recruited from general wards at Addenbrooke's Hospital, Cambridge, UK. Participants were randomly assigned (1:1) by a computer-generated minimisation method to receive closed-loop insulin delivery (using a model-predictive control algorithm to direct subcutaneous delivery of rapid-acting insulin analogue without meal-time insulin boluses) or conventional subcutaneous insulin delivery according to local clinical guidelines. The primary outcome was time spent in the target glucose concentration range of 5·6–10·0 mmol/L during the 72 h study period. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01774565.

Findings Between Feb 20, 2015, and March 24, 2016, we enrolled 40 participants, of whom 20 were randomly assigned to the closed-loop intervention group and 20 to the control group. The proportion of time spent in the target glucose range was 59·8% (SD 18·7) in the closed-loop group and 38·1% (16·7) in the control group (difference 21·8% [95% CI 10·4–33·1]; p=0·0004). No episodes of severe hypoglycaemia or hyperglycaemia with ketonaemia occurred in either group. One adverse event unrelated to study devices occurred during the study (gastrointestinal bleed).

Interpretation Closed-loop insulin delivery without meal-time boluses is effective and safe in insulin-treated adults with type 2 diabetes in the general ward.

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Wellcome Trust–MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK (H Thabit PhD, J M Allen RN, A Lake DipHE, M E Wilinska PhD, Y Ruan MEng, M L Evans MD, A P Coll PhD, R Hovorka PhD); **Wolfson Diabetes Endocrine Clinic, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK** (H Thabit, S Hartnell BSc, M L Evans, A P Coll); **and Department of Paediatrics, University of Cambridge, Cambridge, UK** (J M Allen, M E Wilinska, Y Ruan, R Hovorka)

Correspondence to:
Dr Roman Hovorka, University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Wellcome Trust–MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
rh347@cam.ac.uk

Introduction

The prevalence of hyperglycaemia in hospital inpatients is increasing and poses a common clinical problem because of the rising prevalence of type 2 diabetes.[1,2] Inpatient hyperglycaemia is a widely recognised marker of poor prognosis and is associated with increased morbidity, mortality, length of stay, and health-care costs.[3,4] Guidelines for management of hyperglycaemia in inpatients outside the critical care setting have been proposed,[5] but implementation is challenging and varied because of increased workload burden on ward staff and fear of hypoglycaemia. Development of effective and safe treatments that also reduce staff workload in the general ward is needed.

An automated system linking continuous glucose monitoring and insulin delivery could be a potential solution.[6] Closed-loop insulin delivery, known as the artificial pancreas, is an emerging approach in which a control algorithm autonomously increases and decreases subcutaneous insulin delivery on the basis of real-time sensor glucose concentrations, thus approximating physiological insulin delivery.[7] Studies of closed-loop insulin delivery at home in patients with type 1 diabetes have shown the safety and feasibility of the approach in improving glycaemic control and reducing the risk of hypoglycaemia.[8,9]

A closed-loop insulin delivery system has been shown to be safe and feasible in insulin-naive patients with type 2 diabetes in a controlled research facility setting.[10] We investigated the efficacy and safety of automated closed-loop insulin de livery without meal-time boluses compared with conventional subcutaneous insulin therapy in patients with type 2 diabetes in the general ward.

Methods

Study design and participants

In this single-centre, open-label, parallel-design controlled trial, we recruited participants from general wards at Addenbrooke's Hospital, Cambridge, UK. Inclusion criteria were age 18 years or older, diagnosis of type 2 diabetes as defined by WHO for at least 1 year, and treatment with insulin with or without other glucose-lowering therapy. Exclusion criteria were treatment in intensive care unit, unstable or end-stage cardiac and renal disease including dialysis, pregnancy or breastfeeding, planned surgery during study period, and any physical or psychological disease or medication(s)

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2006 and June 22, 2016, with the search terms ("closed-loop" OR "artificial pancreas") AND ("type 2 diabetes" OR "inpatient hyperglycaemia" OR "stress hyperglycaemia" OR ("hospital" AND "hyperglycaemia")) to identify other novel methods in the management of hyperglycaemia in inpatients. Apart from intravenous closed-loop insulin delivery in intensive care settings, no studies of fully closed-loop subcutaneous insulin delivery in the non-critical settings have been published to date.

Added value of this study

We are not aware of any other study assessing automated fully closed-loop insulin delivery without meal-time boluses in adults with insulin-treated type 2 diabetes in the non-critical care setting. Our results showed a higher proportion of time spent in the target glucose range and reduced glucose variability with closed-loop insulin delivery compared with conventional therapy, without changing the total daily insulin dose or the time spent in hypoglycaemia. Reduction in overnight mean glucose concentration by closed-loop insulin delivery was achieved without increasing the risk of nocturnal hypoglycaemia. Taken together, our findings suggest that an automated closed-loop insulin delivery system can potentially provide health-care professionals with a valuable clinical tool to manage inpatient hyperglycaemia safely and effectively while possibly reducing workload.

Implications of all the available evidence

Guidelines for the management of hyperglycaemia in inpatients have been published, with increased focus on integrated glycaemic management systems and education of health-care providers. Data from several inpatient audits and studies show that implementation in clinical practice is challenging because of the increasing workload on staff and the accelerating increase in the prevalence of diabetes. Technology remains underused in non-critical care management of inpatient hyperglycaemia. Further studies are needed to assess the potential of closed-loop insulin delivery and other technological approaches to improve clinical outcomes including assessing the effect on morbidity and mortality.

likely to interfere with the conduct of the study or interpretation of study results. Participants provided written informed consent before the start of study-related procedures. The study protocol was approved by the East of England Central Cambridge Ethics Committee.

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive fully automated closed-loop insulin delivery or conventional insulin therapy. Randomisation was done by a minimisation method using Minim randomisation software,[11] which is a biased coin approach with a probability of 0·7–0·8 to allocating the best-fitting treatment. Randomisation was stratified according to HbA_{1c}, BMI, and pre-study total insulin dose to ensure balance between the two groups. Investigators analysing study data were not masked to treatment allocation.

Procedures

Participants' bodyweight, height, and total daily insulin dose were recorded after enrolment. Throughout the study, participants chose standard ward meals at usual meal times in the general ward. No restrictions were placed on consuming other meals and snacks or on usual activity in the general ward. Participants were followed up for a maximum of 72 h.

In the closed-loop insulin delivery group, participants' usual insulin therapy and sulfonylurea medication, if prescribed, were discontinued on the day of closed-loop initiation, all other anti-diabetes medications were continued. A subcutaneous cannula was inserted by the investigator in the abdomen for delivery of insulin lispro (Humalog, Eli Lilly, IN, USA) by an insulin pump (Dana R Diabecare, Sooil, Seoul, South Korea). A subcutaneous, real-time, continuous glucose monitor (Freestyle Navigator II, Abbott Diabetes Care, Alameda, CA, USA) was inserted in the abdomen or upper arm by the investigator and calibrated according to the manufacturer's instructions. After successful sensor calibration when sensor glucose concentrations became available, automated closed-loop glucose control was started by the investigator and continued for 72 h. The low glucose alarm on the continuous glucose monitoring receiver was initially set at a threshold of 3·5 mmol/L.

The FlorenceD2W-T2 automated closed-loop system comprised a model predictive control algorithm (version 0.3.65) residing on a control algorithm device (Dell Latitude 10 Tablet, Dell, TX, USA) linked by a USB cable to the continuous glucose monitoring receiver (FreeStyle Navigator II). The tablet communicated with the study pump (Dana R Diabecare) via the Bluetooth wireless communication protocol.

The control algorithm was initialised with participant's bodyweight and pre-study total daily insulin dose. No prandial insulin boluses were delivered and the control algorithm was not provided with timing or carbohydrate content of meals. Every 12 min, the control algorithm calculated the required insulin infusion rate based on sensor glucose measurements. The study pump was then instructed by wireless communication to alter or maintain insulin delivery rate. The control algorithm adapted to a particular participant by updating model parameters and refining the individual's insulin requirements. The algorithm aimed to achieve glucose concentrations

between 5·8 mmol/L and 7·2 mmol/L and adjusted the actual target threshold depending on accuracy of the model-based glucose predictions and prevailing glucose concentrations. Safety rules limited maximum insulin infusion rate on individual basis based on total daily dose and suspended insulin delivery at sensor glucose concentration of 4·2 mmol/L or lower, or when sensor glucose concentration was rapidly decreasing. In the event of sensor failure or loss of sensor availability, an audible alarm by the continuous glucose monitoring receiver sounded to alert the general ward staff or the research team. If sensor glucose measurements continued to be unavailable for 30 min, the study pump insulin infusion rate reverted to the individual's preprogrammed basal rate. For longer interruptions of sensor glucose measurements, the control algorithm could be provided with capillary glucose measurements to direct insulin delivery.

Once-daily subcutaneous basal insulin glargine (Sanofi, Gentilly, France), at 20% of the participant's pre-study total daily insulin dose, was proposed during risk analysis by the interdisciplinary research team to mitigate against the risk of severe hyperglycaemia associated with ketonaemia in the event of prolonged pump disconnection for specific clinically indicated procedures such as MRI, when insulin pump use is contraindicated. This approach was chosen because no studies of closed-loop insulin delivery had been done in this population of patients, practical information was missing within the general ward setting to inform potential safety mitigation, and the dose administered was unlikely to affect efficacy outcomes. The basal insulin dose was kept constant and not titrated throughout the study period. Point-of-care capillary glucose measurements (Nova Stat Strip, Nova Biomedical, MA, USA) were taken by nursing ward staff according to usual clinical practice. These measurements were not used to inform or change insulin delivery rate. At the end of the closed-loop period, participants completed a brief questionnaire providing feedback on satisfaction of glucose control while receiving the closed-loop intervention, such as wearability and mobility with the devices, trust of the closed-loop device to deliver insulin, and whether they would recommend the closed-loop intervention to others. Participants' usual insulin therapy and, as appropriate, sulfonylurea medication was re-started at the end of the closed-loop intervention.

In the conventional insulin therapy group, participants' usual insulin and other antihyperglycaemic therapy was continued throughout the 72 h study period. A continuous glucose monitoring receiver (Freestyle Navigator II) was modified to mask sensor glucose concentrations to the participant, investigators, and ward staff. The continuous glucose monitoring sensor was inserted in the general ward by the clinical investigator on the first day of the study and calibrated according to the manufacturer's instructions. Point-of-care capillary glucose measurements were taken by nursing ward staff (Nova Stat Strip). Participants' glucose control was managed by the clinical

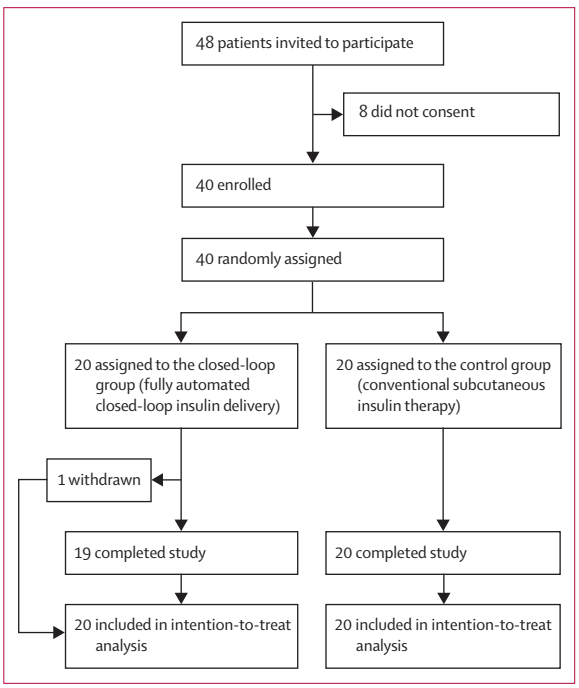

Figure 1: **Trial profile**

	Closed-loop (n=20)	Control (n=20)
Sex		
Male	15 (75%)	13 (65%)
Female	5 (25%)	7 (35%)
Age (years)	67·7 (10·9)	69·3 (12·6)
BMI (kg/m^2)	34·1 (7·3)	32·2 (7·8)
HbA_{1c} (%)	8·6% (2·3)	9·0% (1·8)
HbA_{1c} (mmol/L)	70 (26)	75 (20)
Duration of diabetes (years)	15·1 (7·6)	15·9 (7·1)
Duration on insulin therapy (years)	8·7 (7·3)	8·3 (5·6)
Total daily insulin (U/kg)	0·5 (0·2)	0·7 (0·4)
Metformin	7 (35%)	8 (40%)
Sulfonylurea	4 (20%)	2 (10%)
GLP-1 therapy	2 (10%)	2 (10%)
Basal insulin alone	6 (30%)	3 (15%)
Basal bolus insulin	7 (35%)	11 (55%)
Premixed insulin	7 (35%)	6 (30%)
Number of injections per day	2·3 (1·3)	3·0 (1·2)
Primary diagnosis		
Infected diabetic foot ulcer	14 (70%)	16 (80%)
Ischaemic diabetic foot	3 (15%)	1 (5%)
Congestive cardiac failure	3 (15%)	1 (5%)
Urinary sepsis	0	2 (10%)

Data are n (%) or mean (SD). GLP-1=glucagon-like peptide-1.

Table 1: **Baseline characteristics**

	Closed-loop (n=20)	Control (n=20)	p value
Time spent at glucose concentration (%)			
5·6–10·0 mmol/L*	59·8% (18·7)	38·1% (16·7)	0·0004
>10·0 mmol/L	30·1% (20·4)	49·1% (24·1)	0·011
>20·0 mmol/L	0·6% (1·8)	0·8% (1·9)	0·66
<5·6 mmol/L	10·1% (13·0)	12·9% (13·3)	0·51
<3·5 mmol/L	0·0% (0·0–0·4)	0·0% (0·0–2·7)	0·35
Mean glucose (mmol/L)	8·9 (1·7)	10·1 (2·1)	0·065
SD of glucose (mmol/L)	2·5 (0·9)	3·3 (0·8)	0·007
CV of glucose (%)	27·9% (8·2)	33·4% (8·1)	0·042
Between-day CV of glucose (%)	24·9% (39·0)	24·4% (17·2)	0·97
AUC_{day} <3·5mmol/L (mmol/L×min)	0·0 (0·0–4·1)	0·0 (0·0–80·4)	0·36
Number of events with capillary glucose >20 mmol/L	0	1	1·0
Number of events with capillary glucose <2·8 mmol/L	1	1	1·0
Total daily insulin dose (U)	62·6 (36·3)	65·9 (39·6)	0·78

Data are mean (SD), or median (IQR), unless otherwise stated. AUC_{day}=area under the curve for a glucose concentration of less than 3·5 mmol/L per 24-h period. CV=coefficient of variation. *Primary endpoint.

***Table 2*: Overall glucose control based on sensor glucose measurements**

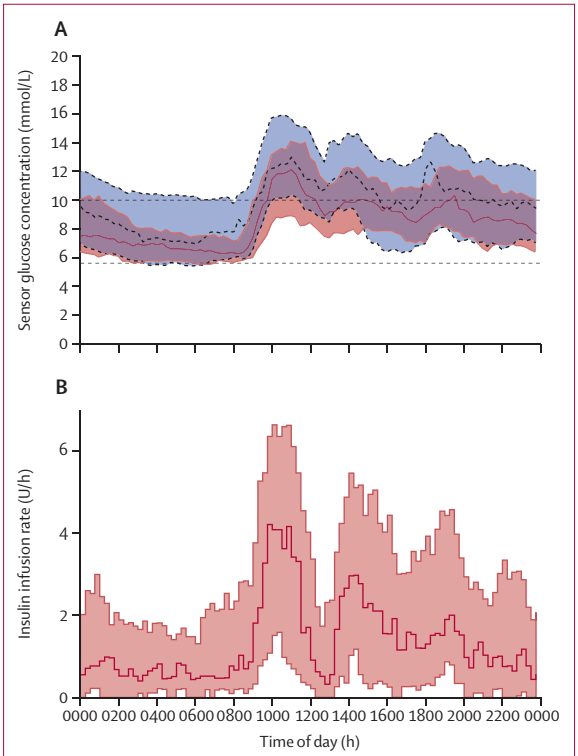

***Figure 2*: Median sensor glucose concentration and insulin delivery**
(A) Median (IQR) sensor glucose concentration during closed-loop insulin delivery (the solid red line and the red shaded area) and control interventions (the dashed black line and the grey shaded area) from 0000 h to 0000 h. The lower and upper limits of the target glucose concentration range of 5·6–10·0 mmol/L are denoted by the horizontal dashed lines. (B) Median (IQR) algorithm-directed insulin delivery during the closed-loop intervention.

team according to local clinical practice. The clinical team was allowed to modify and adjust insulin or other antihyperglycaemic therapy and instigate additional point-of-care capillary glucose measurements as appropriate.

Outcomes

The primary outcome was time spent in the target glucose concentration range of 5·6–10·0 mmol/L during the 72 h study period, as recorded by sensor glucose measurements. Secondary efficacy outcomes were the time spent at glucose concentrations lower than 5·6 mmol/L and greater than 10·0 mmol/L, area under the curve less than 3·5 mmol/L, mean sensor glucose concentration, and total daily insulin dose. Glucose variability was assessed by the SD and the coefficient of variation of sensor glucose concentration using data collected from the whole study period. The between-day coefficient of variation of sensor glucose concentration was calculated from daily mean glucose measurements (0000–0000 h). Daytime (0800–0000 h) and overnight (0000–0800 h) outcomes were calculated for a subset of outcomes to limit multiple comparisons. These outcomes included time in the target range, time spent at concentrations greater than the target range, mean sensor glucose concentration, the SD and the coefficient of variation of sensor glucose concentration, the between-day or between-night coefficient of variation of sensor glucose concentration, and area under the curve less than 3·5 mmol/L using data from the respective periods. The mean pre-meal and pre-bed capillary glucose concentration at each defined time period was calculated for each participant for the whole study period. Safety endpoints included clinically significant hypoglycaemic episodes (<3·5 mmol/L) and other adverse and serious adverse events in accordance with ISO 14155 reporting.

Statistical analysis

Findings from previous studies of closed-loop insulin delivery in patients with type 1 diabetes show that time when sensor glucose concentration is in the target range (primary endpoint) has an SD of 21%.[12–14] We calculated that with 18 participants per group, a difference of 20% between groups could be detected with a power of 80% using two-sided unpaired *t* test at a 5% significance level. A difference of 20% was deemed clinically relevant. The group size was increased to 20 to mitigate against possible differences between type 1 and type 2 diabetes.

The statistical analysis plan was agreed by the investigators in advance. Outcomes were calculated with GStat software (version 2.2) and statistical analyses were done with SPSS (version 21). Because of the sample size, we used an unpaired *t* test to compare variables with the exception of highly skewed variables, when we used a Mann-Whitney *U* test. The number of events related to capillary glucose concentrations of less than 2·8 mmol/L and more than 20·0 mmol/L was tabulated in each

treatment group and compared by use of Fisher's exact test. Values are reported as mean (SD) or median (IQR), unless stated otherwise. All analyses were done by intention to treat. Missing data were not imputed. All p values are two-tailed and values less than 0·05 were considered significant.

This trial is registered with ClinicalTrials.gov, number NCT01774565.

Role of the funding source

The sponsors 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

Between Feb 20, 2015, and March 24, 2016, we recruited 40 participants, of whom 20 were randomly assigned to the closed-loop intervention and 20 to the control group (figure 1). One participant in the closed-loop group was withdrawn from the study because of acute gastrointestinal bleeding unrelated to study procedures, which required immediate surgical intervention and admission to the intensive care unit. Reasons for admission to hospital included infected foot ulcer (30 patients), ischaemic diabetic foot (four patients), congestive cardiac failure (four patients), and urinary tract infection (two patients). Table 1 summarises baseline characteristics (see appendix for details of pre-study treatment including the number of insulin injections per day). The insulin dose in the control group was adjusted by the general ward staff according to standard clinical practice; however, no additional injections or subcutaneous insulin sliding scale were given during the study.

The proportion of time spent in the target glucose concentration range (5·6–10·0 mmol/L) was higher in the closed-loop group than in the control group (59·8% [SD 18·7] *vs* 38·1% [16·7], respectively; difference 21·8% [95% CI 10·4–33·1]; p=0·0004; table 2). Mean sensor glucose concentration was lower, although not significantly, in the closed-loop group than in the control group (p=0·065; table 2; figure 2). The proportion of time spent at concentrations greater than the target range (ie, >10·0 mmol/L) was significantly lower in the closed-loop group than in the control group (difference 19·0% [95% CI 4·7–33·3]; p=0·011), whereas the time spent at concentrations lower than the target range (ie, <5·6 mmol/L) did not differ between groups (p=0·51; table 2). Time spent at concentrations lower than 3·5 mmol/L and burden of hypoglycaemia as measured by area under the curve less than 3·5 mmol/L were low and similar between groups (table 2). Five hypoglycaemic events were detected and notified by low sensor glucose alarm in three patients receiving closed-loop insulin delivery. Oral carbohydrate treatment (20 g) was given during each event by the general ward staff, without the need for intravenous dextrose.

Glucose variability during closed-loop insulin delivery was significantly reduced compared with conventional insulin therapy, as measured by the SD (p=0·007) and the coefficient of variation of sensor glucose concentration (p=0·042; table 2). Participants in the closed-loop group had higher overall time spent within the target range without a significant increase in total daily insulin delivery (p=0·78). Glycaemic outcomes based on pre-meal and pre-bed capillary glucose concentrations did not differ between study groups (table 3).

The proportion of time when overnight (0000–0800 h) glucose was in the target range was significantly higher in the closed-loop group than in the control group (difference 20·1% [95% CI 5·9–34·3]; p=0·007; table 4). The nocturnal burden of hypoglycaemia as measured by area under the curve less than 3·5 mmol/L did not differ between groups (p=0·59). Glucose variability

	Closed-loop (n=20)	Control (n=20)	p value
Pre-breakfast (0500–0800 h)	6·9 (1·3)	7·4 (2·4)	0·16
Pre-lunch (1100–1300 h)	10·9 (3·6)	11·2 (3·1)	0·62
Pre-dinner (1600–1900 h)	9·2 (2·6)	9·8 (3·6)	0·38
Pre-bed (2100–0000 h)	9·3 (3·3)	9·6 (3·7)	0·64

Mean glucose concentrations in mmol/L (SD).

***Table 3*: Pre-meal and pre-bed capillary glucose concentrations**

See Online for appendix

	Closed-loop	Control	p value
Overnight period (0000–0800 h)*			
Time spent at glucose concentration (%)			
5·6–10·0 mmol/L	68·9% (22·1)	48·8% (21·7)	0·007
>10·0 mmol/L	10·9% (16·9)	29·8% (30·6)	0·023
Mean glucose (mmol/L)	7·3 (1·6)	8·2 (2·1)	0·15
SD of glucose (mmol/L)	1·4 (0·7)	2·0 (0·8)	0·030
CV of glucose (%)	19·4% (6·6)	24·9% (10·0)	0·053
Between-night CV of glucose (%)	13·1% (8·8)	33·3% (31·8)	0·011
AUC_{day} <3·5 mmol/L (mmol/L×min)	0·0 (0·0–0·0)	0·0 (0·0–0·3)	0·59
Daytime period (0800–0000h)†			
Time spent at glucose concentration (%)			
5·6–10·0 mmol/L	55·0% (21·3)	34·0% (18·4)	0·002
>10·0 mmol/L	39·6% (24·0)	57·0% (23·4)	0·026
Mean glucose (mmol/L)	9·7 (1·9)	10·9 (2·3)	0·08
SD of glucose (mmol/L)	2·5 (0·9)	3·3 (0·8)	0·011
CV of glucose (%)	25·6% (6·3)	31·3% (9·7)	0·039
Between-day CV of glucose (%)	11·8% (6·3)	19·1% (11·2)	0·018
AUC_{day} <3·5 mmol/L (mmol/L×min)	0·0 (0·0–0·3)	0·0 (0·0–20·2)	0·31

Data are mean (SD) or median (IQR), unless otherwise stated. AUC_{day}=area under the curve for a glucose concentration of less than 3·5 mmol/L per 24-h period *Closed-loop group, n=19 (one participant stopped the study before providing overnight data); control group, n=20. †Closed-loop group, n=20; control group, n=20.

***Table 4*: Overnight (0000–0800 h) and daytime (0800–0000 h) outcomes**

measured by the SD (p=0·030) and the between-night coefficient of variation of sensor glucose concentration (p=0·011) was reduced with closed-loop therapy compared with conventional therapy. Results from the daytime period (0800–0000 h; table 4) showed that the proportion of time spent in the target glucose concentration range was significantly higher in the closed-loop group than in the control group (p=0·002). Daytime glucose variability, as measured by the SD of sensor glucose concentration (p=0·011) and the overall (p=0·039) and between-day (p=0·018) coefficient of variation of sensor glucose concentration, was reduced in the closed-loop group compared with the control group. We noted no significant differences in mean sensor glucose concentration and area under the curve less than 3·5 mmol/L during the daytime period.

Total time of sensor glucose availability was similar in the two groups (appendix). Glucose sensors were replaced seven times in the closed-loop group (five because of sensor failures, two because of MRI scanning procedures) and three times in the control group (twice because of sensor failures, once because of MRI scanning procedure). The insulin pump device was removed on two occasions during the study because of MRI scanning procedures. No insulin pump failures occurred during the study.

No episodes of severe hypoglycaemia or hyperglycaemia with ketonaemia occurred in either group. One adverse event unrelated to study devices occurred in the closed-loop group (gastrointestinal bleed). No serious adverse event occurred in either group. 17 (85%) of 20 participants in the closed-loop group stated that they were happy with their glucose concentrations in hospital during the study and 18 (90%) were happy to have their glucose concentrations controlled automatically by the closed-loop system (figure 3). 19 (95%) would recommend the system to a friend or family member if they were admitted to hospital.

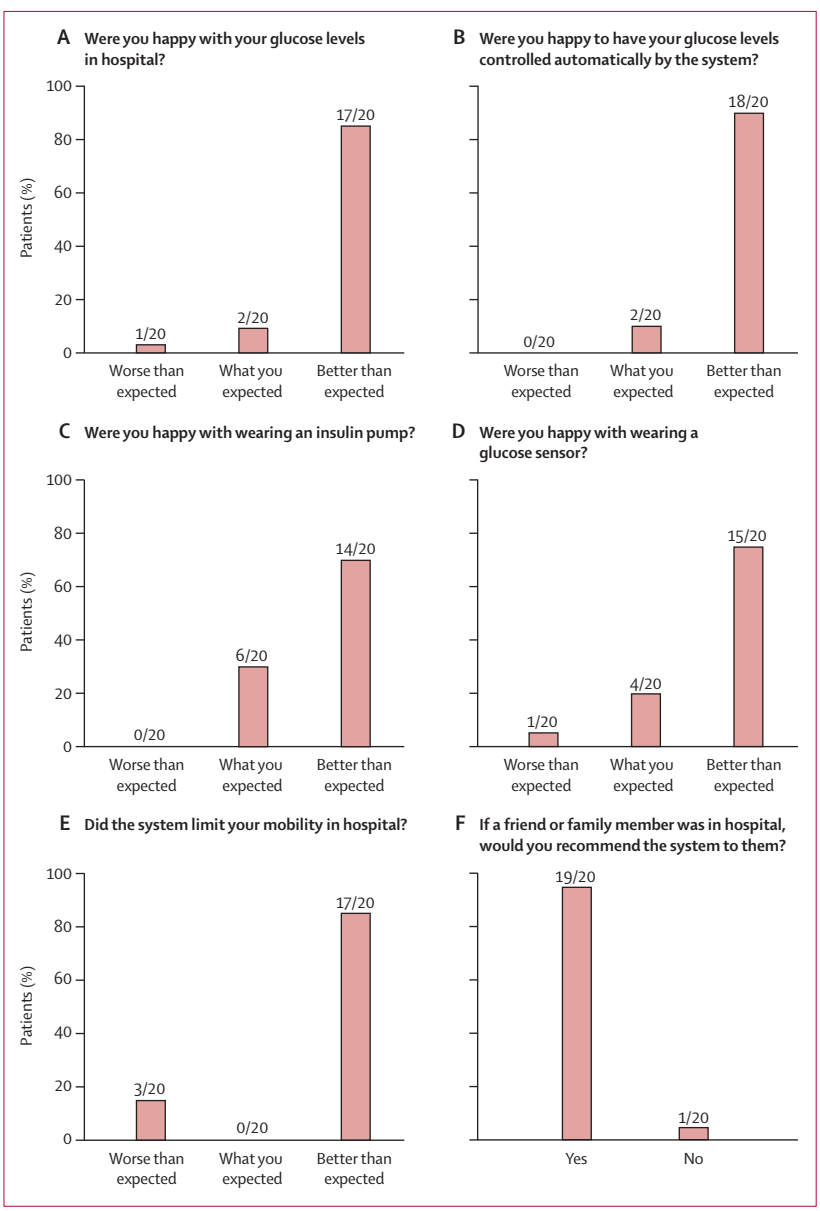

Figure 3: **Participant responses to the questionnaire about closed-loop insulin delivery**

Discussion

Our results suggest that the use of a fully automated closed-loop insulin delivery system in patients with insulin-treated type 2 diabetes in the general ward is safe and feasible. Compared with the local hospital protocol for glucose management, time when sensor glucose concentration was in the target range was significantly improved with the closed-loop delivery system, without increased risk of hypoglycaemia.

Professional societies' recommendations of target glucose concentrations in non-critical care settings (pre-meal blood glucose targets of <5·6 mmol/L, and random blood glucose concentrations of <10·0 mmol/L) are not currently attainable by many health-care institutions.[1,15] These trends of suboptimal glucose control are seen even when speciality input is available.[16] In our study, time within the recommended target glucose range was increased by closed-loop insulin delivery by roughly 22% compared with a matched cohort receiving usual care. This outcome was achieved without an increase in the amount of insulin delivered, thereby further minimising the risk of hypoglycaemia. Although time spent in hypoglycaemia was similar in both groups, it was notably low in the control group. Avoidance and fear of hypoglycaemia is a primary concern of many health-care professionals caring for inpatients with diabetes, which might have contributed to this finding. Inpatient hypoglycaemia, either iatrogenic or disease-related, is associated with poorer outcomes such as increased morbidity and mortality.[17] The length of hospital stay is prolonged by hypoglycaemia, affecting overall health-care

cost.[18] Several vulnerable populations in the general ward are known to be at an increased risk, such as older people (≥65 years) or individuals with poor nutritional intake. Severe hyperglycaemia with ketonaemia in potentially insulin-deficient patients was mitigated by administration of basal insulin at 20% of pre-study insulin dose during the closed-loop intervention. The likelihood of ketonaemia in the studied population is inherently low, however, and we consider that regular administration of basal insulin injections might not be required in future studies.

Measures of sensor glucose variability during closed-loop insulin delivery seem to be consistently reduced compared with during conventional insulin therapy. Glycaemic fluctuations are known to occur in hospital inpatients as a result of nutritional status and intake, as well as changes in insulin sensitivity during the period of illness. The advantage of an automated-control, algorithm-directed insulin delivery system such as ours, compared with conventional insulin therapy, is the finely tuned frequent modulation of insulin delivery according to sensor glucose concentrations, thereby trading variability of insulin delivery with glycaemic consistency. Previous studies, predominantly in critical care settings, have reported a link between increased glucose variability and endothelial dysfunction[19] and mortality.[20] Our study was not statistically powered for these outcomes; thus, large, well designed studies are needed to establish whether reduction in glycaemic variability and improved glucose control by closed-loop insulin delivery, specifically in non-critical care settings, could have clinically meaningful and beneficial effects.

Intravenous closed-loop insulin delivery systems have been studied in intensive care settings.[21–23] The need for intravascular access for insulin delivery in these studies limits use in the non-critical care general ward settings. A randomised study[24] was performed in hospitalised non-critical care type 2 diabetes patients, comparing standard glycaemic management with workflow-integrated algorithm for basal bolus insulin therapy, which ward staff accessed via a tablet device. Over a 7 day period, time in target range (3·9–10 mmol/L) and mean blood glucose levels were significantly improved in the algorithm group. Patients in the algorithm group who applied blinded continuous glucose monitoring, however, had numerous hypoglycaemic events (sensor glucose <3·9 mmol/L) during the daytime. Post-hoc analysis suggests that higher lunchtime blood glucose which required higher correction insulin boluses may have been contributory. The aforementioned computerised glucose management system depends on ward staff input at meal times. Other novel strategies for inpatient glucose control include the use of GLP-1 and DPP-4 inhibitor based therapies, which are thought to have a lower risk of hypoglycaemia due to their glucose-dependent action.[25,26] However adverse effect profiles such as nausea and vomiting may limit their use in hospital, especially in those with swallowing difficulties and at increased risk of aspiration.

The strength of our study is the novel application of an automated closed-loop insulin delivery system in a real-world general ward environment. The closed-loop system used off-the-shelf devices including a commercially available subcutaneous real-time continuous glucose monitor and insulin pump, thereby reducing regulatory complexity and accelerating availability of the system for future clinical use. No prandial insulin delivery was administered, reducing the risk of hypoglycaemia caused by delayed or reduced meal consumption and skipped meals, while also reducing staff workload. In the control group, glucose control was managed according to local hospital guidelines reflecting real-world practice in which wider use of basal-bolus insulin therapy in hospital as recommended by experts in the field is not always feasible or safe.

Our study is limited by a single-centre setting, a short duration, and a predominance of patients with foot ulcers who were approached in view of their expected longer stay in hospital. Another potential limitation is the administration of daily basal insulin glargine in the closed-loop group, and not the control group, instigated during the initial study design phase to mitigate against potential ketonaemia in the event of prolonged pump disconnection. Because no historical data were available for the risk assessment before our study, this precaution was implemented until corroborative data related to closed-loop use in this unique population were available. Supportive findings from the present work provide justification to omit daily basal insulin glargine from future studies as a pragmatic measure to reduce staff workload without the need for a pilot study. The dose of basal insulin glargine given in our study, maintained at a constant dose throughout, is estimated to account for between 10% and 20% of the total (the sum of endogenous and exogenous) insulin concentration in type 2 diabetes,[21] thus negligible in terms of efficacy in view of the adaptive nature of the closed-loop algorithm, which needs to cope with more than 30-times greater changes in insulin needs. Finally, the availability of low sensor glucose alarms in the closed-loop group might have potentially mitigated against hypoglycaemia events compared with the control group. Continuous glucose monitoring is currently not recommended as part of usual clinical care in the general ward, while being an integral part of closed-loop systems. Therefore, low sensor glucose alarms in addition to automated modulation of insulin delivery based on real-time sensor glucose concentrations, could support the incremental benefit of the closed-loop intervention in the general ward.

Although no formal feedback was collected from the ward staff, there was no interruption to the ward workflow and patients' usual ward-related activities from the closed-loop intervention. Patient feedback from closed-loop use suggests that the system acceptability was high, with most patients happy to have their glucose control managed autonomously by the closed-loop

system, and suggest a substantial level of trust by patients. The absence of feedback from the control group limits interpretation on whether the closed-loop intervention improved patients' experience and perception of glucose control management in hospital.

In conclusion, our findings show that automated closed-loop insulin delivery without meal-time boluses, or provision of information about meals to the control algorithm, in adults with insulin-treated type 2 diabetes is safe and feasible in the non-critical care setting. However, further and longer studies are warranted.

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, HT, SH, MLE, and APC co-designed the studies. HT, SH, JMA, and AL were responsible for screening and enrolment of participants and arranged informed consent from the participants. HT, SH, and JMA provided patient care. MEW managed randomisation. HT, MEW, and YR performed or supported data analysis, including the statistical analyses. RH designed and implemented the glucose controller. HT, RH, MEW, MLE, and APC contributed to the interpretation of the results. All authors critically reviewed the report. No writing assistance was provided.

Declaration of interests

SH serves as a consultant for Novo Nordisk and for the ONSET group, and reports having received speaker and training honoraria from Medtronic. MLE reports having received speaker honoraria from Abbott Diabetes Care, Novo Nordisk, and Animas; and serving on advisory panels for Novo Nordisk, Abbott Diabetes Care, Medtronic, Roche, and Cellnovo. RH reports having received speaker honoraria from Eli Lilly and Novo Nordisk; serving on advisory panels for Eli Lilly and Novo Nordisk; receiving license fees from B Braun and Medtronic; and having served as a consultant to B Braun. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. RH and MEW report patents and patent applications relevant to the present work. All other authors declare no competing interests.

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References

1 Health and Social Care Information Centre (HSCIC), NHS. National diabetes inpatient audit. 2011. http://content.digital.nhs.uk/catalogue/PUB20206/nati-diab-inp-audi-15-nat-rep.pdf (accessed Oct 27 2016).

2 Wexler DJ, Meigs JB, Cagliero E, Nathan DM, Grant RW. Prevalence of hyper- and hypoglycemia among inpatients with diabetes: a national survey of 44 U.S. hospitals. *Diabetes Care* 2007; **30:** 367–69.

3 Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87:** 978–82.

4 Dhatariya K. Should inpatient hyperglycaemia be treated? *BMJ* 2013; **346:** f134.

5 Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97:** 16–38.

6 Thabit H, Hovorka R. Glucose control in non-critically ill inpatients with diabetes: towards closed-loop. *Diabetes Obes Metab* 2014; **16:** 500–09.

7 Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. *Nat Rev Endocrinol* 2011; **7:** 385–95.

8 Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. *N Engl J Med* 2015; **373:** 2129–40.

9 Kropff J, Del Favero S, Place J, et al. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol* 2015; **3:** 939–47.

10 Kumareswaran K, Thabit H, Leelarathna L, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. *Diabetes Care* 2014; **37:** 1198–203.

11 Evans S, Day S, Royston P. Minim: minimisation program for allocating patients to treatments in clinical trials. http://www-users.york.ac.uk/~mb55/guide/minimins.doc (accessed Oct 4, 2016).

12 Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010; **375:** 743–51.

13 Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ* 2011; **342:** d1855.

14 Hovorka R, Nodale M, Haidar A, Wilinska ME. Assessing performance of closed-loop insulin delivery systems by continuous glucose monitoring: drawbacks and way forward. *Diabetes Technol Ther* 2013; **15:** 4–12.

15 Boord JB, Greevy RA, Braithwaite SS, et al. Evaluation of hospital glycemic control at US academic medical centers. *J Hosp Med* 2009; **4:** 35–44.

16 Neubauer KM, Schaupp L, Plank J, et al. Failure to control hyperglycemia in noncritically ill diabetes patients despite standard glycemic management in a hospital setting. *J Diabetes Sci Technol* 2013; **7:** 402–09.

17 Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 2009; **32:** 1153–57.

18 Ahmann A. Reduction of hospital costs and length of stay by good control of blood glucose levels. *Endocr Pract* 2004; **10** (suppl 2)**:** 53–56.

19 Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; **57:** 1349–54.

20 Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; **36:** 3008–13.

21 Thabit H, Kumareswaran K, Haidar A, et al. Glucose turnover after replacement of usual therapy by insulin in insulin-naive type 2 diabetes subjects. *J Clin Endocrinol Metab* 2014; **99:** 2225–32.

22 Leelarathna L, English SW, Thabit H, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. *Crit Care* 2013; **17:** R159.

23 Okabayashi T, Nishimori I, Maeda H, Yamashita K, Yatabe T, Hanazaki K. Effect of intensive insulin therapy using a closed-loop glycemic control system in hepatic resection patients: a prospective randomized clinical trial. *Diabetes Care* 2009; **32:** 1425–27.

24 Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes Care* 2014; **37:** 1516–24.

25 Mader JK, Neubauer KM, Schaupp L, et al. Efficacy, usability and sequence of operations of a workflow-integrated algorithm for basal-bolus insulin therapy in hospitalized type 2 diabetes patients. *Diabetes Obes Metab* 2014; **16:** 137–46.

26 Abuannadi M, Kosiborod M, Riggs L, et al. Management of hyperglycemia with the administration of intravenous exenatide to patients in the cardiac intensive care unit. *Endocr Pract* 2013; **19:** 81–90.

27 Umpierrez GE, Korytkowski M. Is incretin-based therapy ready for the care of hospitalized patients with type 2 diabetes?: Insulin therapy has proven itself and is considered the mainstay of treatment. *Diabetes Care* 2013; **36:** 2112–17.