

Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial



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Summary

Background Closed-loop systems link continuous glucose measurements to insulin delivery. We aimed to establish whether closed-loop insulin delivery could control overnight blood glucose in young people.

Methods We undertook three randomised crossover studies in 19 patients aged 5–18 years with type 1 diabetes of duration 6.4 years (SD 4.0). We compared standard continuous subcutaneous insulin infusion and closed-loop delivery (n=13; APCam01); closed-loop delivery after rapidly and slowly absorbed meals (n=7; APCam02); and closed-loop delivery and standard treatment after exercise (n=10; APCam03). Allocation was by computer-generated random code. Participants were masked to plasma and sensor glucose. In APCam01, investigators were masked to plasma glucose. During closed-loop nights, glucose measurements were fed every 15 min into a control algorithm calculating rate of insulin infusion, and a nurse adjusted the insulin pump. During control nights, patients' standard pump settings were applied. Primary outcomes were time for which plasma glucose concentration was 3.91–8.00 mmol/L or 3.90 mmol/L or lower. Analysis was per protocol. This trial is registered, number ISRCTN18155883.

Findings 17 patients were studied for 33 closed-loop and 21 continuous infusion nights. Primary outcomes did not differ significantly between treatment groups in APCam01 (12 analysed; target range, median 52% [IQR 43–83] closed loop vs 39% [15–51] standard treatment, $p=0.06$; ≤ 3.90 mmol/L, 1% [0–7] vs 2% [0–41], $p=0.13$), APCam02 (six analysed; target range, rapidly 53% [48–57] vs slowly absorbed meal 55% [37–64], $p=0.97$; ≤ 3.90 mmol/L, 0% [0–4] vs 0% [0–0], $p=0.16$), and APCam03 (nine analysed; target range 78% [60–92] closed loop vs 43% [25–65] control, $p=0.0245$, not significant at corrected level; ≤ 3.90 mmol/L, 10% [2–15] vs 6% [0–44], $p=0.27$). A secondary analysis of pooled data documented increased time in the target range (60% [51–88] vs 40% [18–61]; $p=0.0022$) and reduced time for which glucose concentrations were 3.90 mmol/L or lower (2.1% [0.0–10.0] vs 4.1% [0.0–42.0]; $p=0.0304$). No events with plasma glucose concentration lower than 3.0 mmol/L were recorded during closed-loop delivery, compared with nine events during standard treatment.

Interpretation Closed-loop systems could reduce risk of nocturnal hypoglycaemia in children and adolescents with type 1 diabetes.

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Introduction

Type 1 diabetes is one of the most common chronic childhood diseases¹ and incidence has doubled during the past 10 years.² Children and adolescents need life-long insulin treatment to achieve glucose control that is sufficient to prevent long-term complications.³ However, intensive insulin therapy is associated with increased risk of hypoglycaemia, which is the most feared complication for children and their parents, impeding efforts to achieve recommended glucose concentrations.⁴ Technological developments in monitoring of glucose concentrations and methods for continuous insulin administration could reduce this risk.

Continuous monitoring devices measure interstitial glucose as a marker of changes in blood glucose concentration.⁵ Although still less accurate than are blood

glucose meters, devices have improved glucose control.⁶ The established technique of continuous subcutaneous insulin infusion uses a portable electromechanical pump to mimic non-diabetic insulin delivery, infusing insulin at preselected rates—which are slow basal rates with patient-activated boosts at mealtimes.⁷ Continuous glucose monitoring devices and insulin pumps can be combined to form closed-loop systems. Insulin is then delivered according to real-time sensor glucose data, as directed by a control algorithm, rather than at pre-programmed rates.

Few closed-loop prototypes have been developed^{8–10} and progress has been hindered by suboptimum accuracy and reliability of monitoring devices, slow absorption of subcutaneously administered rapid-acting insulin analogues, and inadequate control algorithms.⁸

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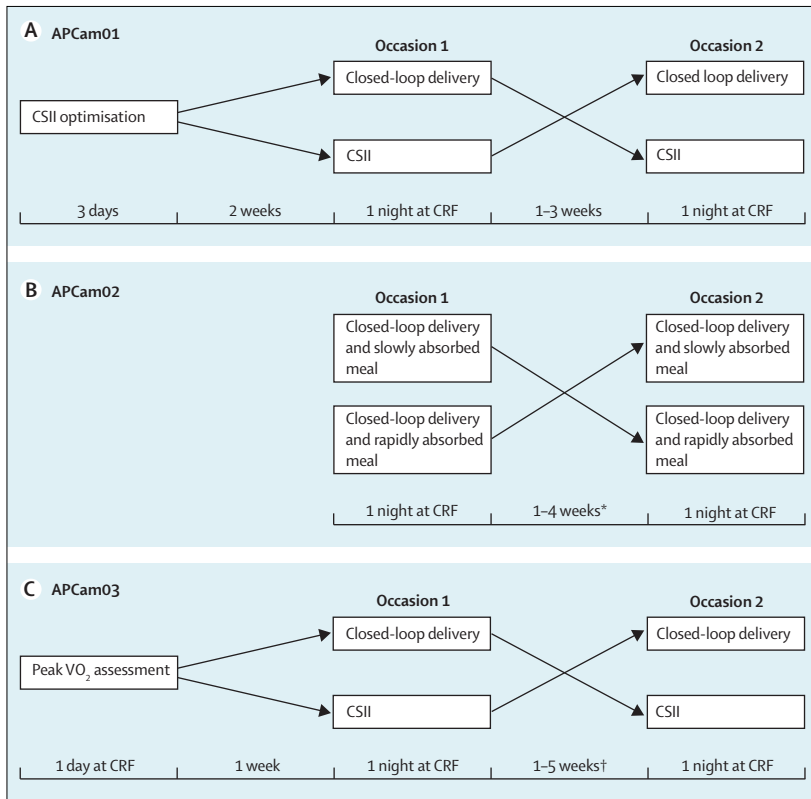


Figure 1: Trial design
 (A) APCam01 (12 nights per treatment). (B) APCam02 (six nights per treatment). (C) APCam03 (nine nights per treatment). APCam=Artificial Pancreas Project at Cambridge. CSII=continuous subcutaneous insulin infusion. CRF=clinical research facility. Peak VO_2 =maximum oxygen uptake. Planned 1–3 weeks, but for logistical reasons extended to 24 and 27 days in two patients (*) and to 35 and 36 days in two patients (†).

We believe that these drawbacks can be overcome with commercially available continuous glucose monitoring and pump delivery systems in combination with advanced control algorithms, such as those that are based on model-predictive control.¹¹ We aimed to establish whether closed-loop systems reduce risk of nocturnal hypoglycaemia and achieve good glucose control in children and adolescents, even after variable evening meal intake and differing exercise patterns.

Methods

Patients and study design

From April, 2007, to September, 2008, children and adolescents were enrolled in three studies at the Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital (Cambridge, UK). Inclusion criteria were diagnosis of type 1 diabetes as defined by WHO for at least 6 months or confirmed C-peptide negative, and treatment by continuous subcutaneous insulin infusion for at least 3 months. Exclusion criteria were recurrent severe hypoglycaemic unawareness or clinically significant nephropathy, neuropathy, or proliferative retinopathy. Participants and their caregivers were provided with age-appropriate patient

information sheets. Participants aged 16 years and older and parents or guardians of patients aged younger than 16 years signed the consent form. Study protocols were approved by the Cambridge Ethics Committee. Studies were done in accordance with the Declaration of Helsinki.

Figure 1 shows the randomised crossover design of the three studies. We compared the closed-loop system with standard continuous subcutaneous insulin infusion (Artificial Pancreas Project at Cambridge [APCam] 01), assessed effects of a variable-content large evening meal (APCam02), and investigated effects of moderate-intensity evening exercise (APCam03).

Randomisation and masking

The allocation sequence was generated by LJC and MEW with computer-generated random code and placed in sealed envelopes. Neither block nor stratification was used. Participants were masked to plasma and sensor glucose data. In APCam01, investigators were masked to plasma glucose data. No other masking was applied.

Procedures

In APCam01, 13 patients aged 5–18 years were assigned to be treated with overnight closed-loop delivery or standard treatment on two occasions 1 to 3 weeks apart. 2 weeks before the first study occasion, insulin pump delivery was optimised by analysing 72 h of non-real-time sensor glucose. On both occasions, patients consumed a self-selected meal (mean 87 g [SD 23] carbohydrates) at 18.00 accompanied by prandial insulin (9 U [5]) calculated according to patients' insulin-to-carbohydrate ratio and capillary fingerstick glucose value. Meals were identical on both nights. Closed-loop control was applied between 20.00 and 08.00. On continuous insulin infusion nights, patients' standard insulin pump settings were applied. Between study nights, self-adjustment of insulin delivery was allowed.

The first seven patients aged 12–18 years recruited for APCam01 were recruited for APCam02 and studied on two further occasions, 1 to 4 weeks apart. At 18.00 on both nights, patients consumed either a rapidly or slowly absorbed large meal selected from a list of standard meals differing in glycaemic load (rapid, 113 [29], vs slow, 40 [8]; $p=0.001$, paired t test) but matched for carbohydrates (129 g [34] vs 129 g [34]; p value not significant). The carbohydrate amount corresponded to largest meal eaten during the preceding 3 months. Prandial insulin doses were similar (17 U [6] vs 17 U [7]) and were calculated according to patients' insulin-to-carbohydrate ratio and sensor glucose concentrations. Closed-loop delivery was done from 18.30 to 08.00.

In APCam03, ten postpubertal patients aged 12–18 years were assigned to be studied on two occasions. Six were new patients, not participating in APCam01 or

APCam02, and four were the first patients to be recruited for APCam01 who were postpubertal and willing to participate. A week before the first night, a ramped treadmill protocol was used to estimate maximum oxygen uptake (peak VO_2).¹² Subsequently, patients were studied after identical exercise protocols with closed-loop delivery or continuous insulin infusion. At 16.00, patients ate a light meal chosen from a list of standard snacks (45 g [13] carbohydrates) accompanied by prandial bolus calculated from their insulin-to-carbohydrate ratio and sensor glucose concentrations. They exercised at 55% of peak VO_2 on a treadmill from 18.00 until 18.45 with a 5-min rest at 18.20. Insulin was then delivered by closed loop between 20.00 and 08.00. On continuous insulin infusion nights, patients' standard pump settings were applied.

On every study occasion, on patients' arrival at the clinical research facility a sampling cannula was inserted in an antecubital vein. Venous samples were obtained every 15 min for glucose estimation and every 30 min for insulin assay from 17.00 (or from 16.00 in APCam02) until 08.00. These data were not used to calculate or change insulin doses during continuous infusion or closed-loop delivery—doses were dependent on sensor glucose readings only.

In APCam01, Guardian Real-Time (GRT; Medtronic MiniMed, Northridge, CA, USA) was used to measure real-time subcutaneous glucose during closed-loop control. During continuous insulin infusion, non-real-time subcutaneous glucose was recorded by Continuous Glucose Monitoring System Gold (CGMS Gold; Medtronic MiniMed, Northridge, CA, USA). In APCam02 and APCam03, FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA) was used. Accuracy of the devices, measured as relative absolute difference between sensor glucose and paired plasma glucose divided by plasma glucose, was 9.2% (4.3–16.7) for GRT and 7.6% (3.8–14.1) for CGMS. These two devices were calibrated at the clinical research facility every 6 h from 17.00 with venous glucose concentrations measured with Yellow Springs Instrument (YSI) analyser. The relative absolute difference was 12.7% (5.6–21.9) for Navigator, as calibrated with capillary fingersticks as per manufacturer's instructions. Accuracy of GRT in our investigations was slightly better than reported data,¹³ which is at least partly accounted for by highly accurate calibration of the device. Accuracy of Navigator was similar to reported data.¹³

On arrival at the clinical research facility, patients' insulin pumps were disconnected and the study pump Deltec Cozmo (Smiths Medical, St Paul, MN, USA) connected to the established subcutaneous infusion site delivering rapid-acting insulin analogue Aspart (Novo Nordisk, Bagsvaerd, Denmark). Plasma glucose was measured by YSI2300 STAT Plus Analyser (YSI, Farnborough, UK). Plasma insulin was measured with an immunochemiluminometric assay (Invitron,

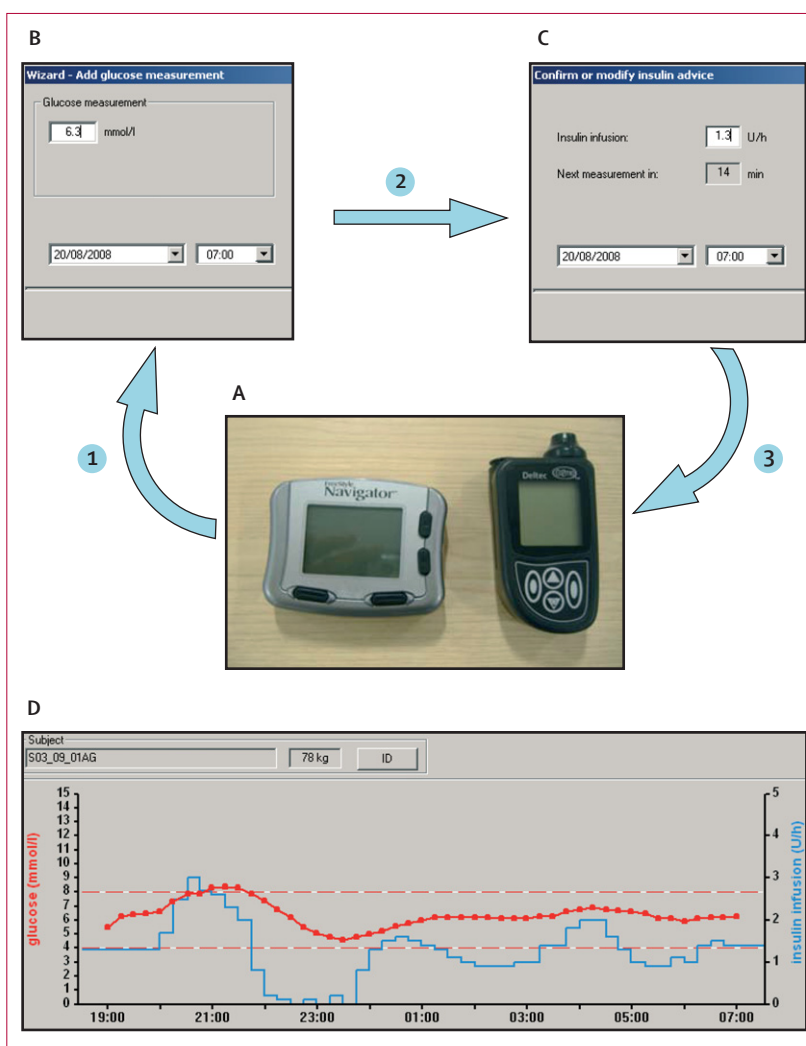


Figure 2: Closed-loop algorithm

Manual operation of the closed-loop system consists of three steps repeated every 15 min. Step 1: research nurse reads sensor glucose from continuous glucose monitoring (CGM) display (A) and types glucose concentration in a workflow wizard running on a laptop (B). Step 2: the wizard calls the control algorithm, which computes the insulin infusion rate that is subsequently displayed by the workflow wizard (C). Step 3: research nurse manually sets infusion rate on the insulin pump (A). Freestyle Navigator CGM device used in APCam02 and APCam03 and Deltec Cozmo insulin pump are shown (A). Data obtained during closed-loop are shown on the graphical user interface (D). Plot shows sensor glucose (red circle) and insulin infusion (blue line) obtained during a sample study in APCam03. Dashed red lines show target glucose range. Reproduced by permission of Smiths Medical ASD Inc (St Paul, MN, USA) and Abbott Diabetes Care (Alameda, CA, USA).

Monmouth, UK; intra-assay coefficient of variation [CV] 4.7%; interassay CV 7.2–8.1%).

We used an adaptive algorithm for the closed-loop system that was based on model-predictive control.¹¹ Every 15 min, real-time sensor glucose was entered into the algorithm, which calculated infusion rates for the insulin pump which was manually adjusted by a nurse (figure 2). The algorithm adopted a compartment model of glucose kinetics¹⁴ describing the effect of rapid-acting insulin analogue and the carbohydrate content of meals on sensor glucose excursions. It was initialised with a patient's weight, total daily insulin dose, and basal

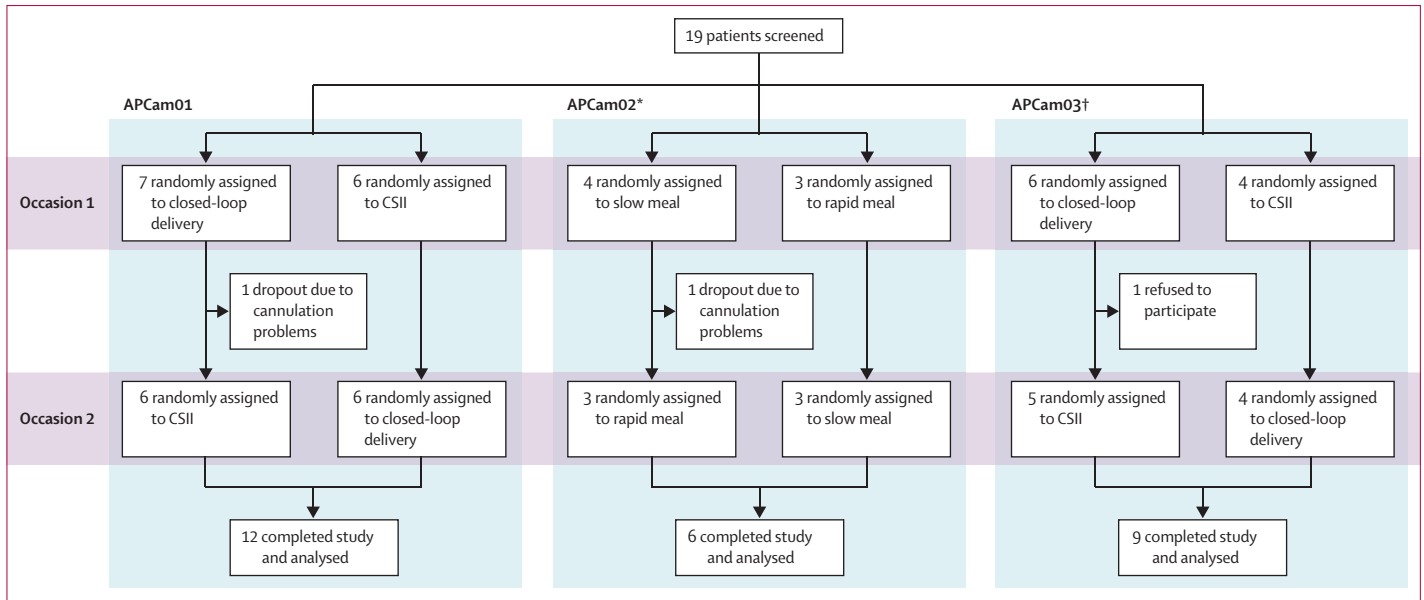


Figure 3: Trial profile

APCam=Artificial Pancreas Project at Cambridge. *All seven patients who entered APCam02 participated in APCam01. †Two who entered APCam03 participated in both APCam01 and 02; another two participated in APCam01 only.

	APCam01 (n=12)	APCam02 (n=6)	APCam03 (n=9)	APCam01-03 (n=17)
Sex (male)	7	1	3	8
Age (years)	13.4 (4.3)	15.0 (2.2)	14.2 (2.1)	13.5 (3.6)
BMI (kg/m ²)	21.9 (4.2)	22.9 (4.3)	19.8 (2.9)	21.0 (4.0)
HbA _{1c} (%)	8.7% (2.0)	9.1% (2.4)	7.8% (1.0)	8.5% (1.8)
Duration of diabetes (years)	7.0 (4.5)	6.4 (4.4)	5.6 (3.2)	6.4 (4.0)
Duration on pump (years)	1.9 (1.1)	1.5 (0.9)	2.0 (1.2)	1.9 (1.1)
Total daily insulin (U/kg per day)	0.89 (0.27)	0.96 (0.16)	0.93 (0.23)	0.92 (0.24)

Data are mean (SD) or number. BMI=body-mass index. HbA_{1c}=haemoglobin A_{1c}. APCam=Artificial Pancreas Project at Cambridge.

Table 1: Patient characteristics

insulin requirements. In real time, sensor glucose measurements were used to update two model variables—an endogenous glucose flux correcting for errors in model-based predictions and carbohydrate bioavailability. Several competing models differing in rate of subcutaneous insulin absorption and carbohydrate absorption profile were run in parallel.¹⁵ A combined model forecasted plasma glucose excursions during a 2.5-h prediction horizon. Insulin infusion was calculated to achieve target glucose, which was set at 5.8 mmol/L, but was flexible and could increase up to 7.3 mmol/L if previous predictions were inaccurate. Safety rules could reduce insulin infusion to prevent overdosing. Algorithm version 0.00.02 to 0.01.05 was used.

Primary outcomes were time for which plasma glucose concentration was in the target range (3.91–8.00 mmol/L) and lower than the target range (≤3.90 mmol/L) between 20.00 and 08.00 for APCam01

and APCam03, and from 18.30 for APCam02. Secondary outcomes were mean glucose concentration, time for which glucose concentration was higher than 8.0 mmol/L, mean rate of insulin infusion, and mean plasma insulin concentration. Low blood-glucose index assessed duration and extent of hypoglycaemia and was calculated as an average of transformed glucose measurements progressively increasing at low glucose concentrations.¹⁶ Grade A and B assessed effectiveness and grade E and F assessed safety with glycaemic control grading,¹⁷ which defines six glucose bands, A to F; band A implies excellent control and band F unsafe control. Secondary outcomes were calculated between start of closed-loop control and 08.00, and between midnight and 08.00.

Statistical analysis

APCam01 was an exploratory investigational study. Power calculations were not done for APCam02, because this was primarily a safety study and formally an extension of APCam01. In APCam03, closed-loop control was expected to reduce time spent at plasma glucose concentrations lower than 3.90 mmol/L by a mean of 38% (SD 35). Nine patients provided 80% power at 5% significance level to detect this difference. For every outcome measure, a repeated measures regression model compared alternative treatments adjusting for a period effect. Because many outcomes were not normally distributed, we calculated significance levels using a permutation test, which is a non-parametric resampling procedure¹⁸ in which the null hypothesis of exchangeability is tested by comparison of the estimated treatment effect from the regression

	APCam01 (n=12*)			APCam03 (n=9*)			APCam01 and 03 combined (n=21†)		
	CL	CSII	p value	CL	CSII	p value	CL	CSII	p value
Time when plasma glucose in target range (%)	52% (43–83)	39% (15–51)	0.06‡	78% (60–92)	43% (25–65)	0.0245‡	60% (51–88)	40% (18–61)	0.0022§
Time when plasma glucose ≤3.90 mmol/L (%)	1.0% (0.0–7.1)	2.0% (0.0–41.0)	0.13‡	10.0% (2.0–15.0)	6.1% (0.0–44.0)	0.27‡	2.1% (0.0–10.0)	4.1% (0.0–42.0)	0.0304§

Data are median (interquartile range). Plasma glucose target range was 3.91–8.00 mmol/L. Data for APCam01 and 03 presented separately are from primary analysis; pooled data are results of secondary analysis. CL=closed-loop delivery. CSII=continuous subcutaneous insulin infusion. APCam=Artificial Pancreas Project at Cambridge. *Number of patients. †Number of nights per treatment. ‡Bonferroni correction used—ie, p value of less than 0.0125 (0.05÷4) regarded as significant. §No formal adjustment for multiple comparisons was done for secondary comparisons.

Table 2: Outcomes of APCam01 and APCam03

	APCam01			APCam03		
	CL (n=12)	CSII (n=12)	p value	CL (n=9)	CSII (n=9)	p value*
From start of closed-loop†						
Plasma glucose at start (mmol/L)	10.2 (3.6)	11.4 (5.3)	0.66	6.8 (2.2)	11.7 (5.9)	0.0290
Overnight glucose (mmol/L)	7.8 (1.7)	8.3 (3.4)	0.75	5.9 (1.3)	7.8 (4.1)	0.28
SD of overnight glucose (mmol/L)	2.2 (1.6–3.0)	2.1 (1.5–2.7)	0.87	0.9 (0.8–1.5)	2.4 (1.8–3.6)	0.06
Time for which plasma glucose ≤3.5 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–21.0)	0.13	4.1% (0.0–6.1)	0.0% (0.0–28.0)	0.19
Time for which plasma glucose >8.0 mmol/L (%)	43% (12–57)	36% (19–74)	0.59	0% (0–25)	31% (10–54)	0.09
LBG1	0.4 (0.0–2.3)	1.1 (0.1–6.3)	0.14	2.8 (0.9–3.1)	3.6 (0.6–7.4)	0.20
Grade A and B (%)	36% (22–65)	26% (10–41)	0.18	60% (51–83)	16% (10–32)	0.0104
Grade E and F (%)	0.0% (0.0–6.1)	8.0% (0.0–35.1)	0.10	0.0% (0.0–1.4)	13.7% (6.4–41.9)	0.0188
Insulin infusion (U/h)	1.2 (0.6–2.0)	1.1 (0.6–1.8)	0.40	0.8 (0.6–1.0)	0.9 (0.7–1.2)	0.42
Plasma insulin concentration (pmol/L)	207 (149–368)	238 (148–349)	0.80	199 (148–453)	229 (146–469)	0.23
After midnight‡						
Time for which plasma glucose in target range (%)	76% (61–89)	35% (1.5–71.0)	0.0351	91% (76–100)	35% (13–64)	0.0268
Time for which plasma glucose ≤3.90 mmol/L (%)	1.5% (0.0–11.0)	3.0% (0.0–61.0)	0.13	3.0% (0.0–15.0)	9.1% (0.0–42.0)	0.22
Overnight glucose (mmol/L)	6.8 (1.6)	7.3 (3.8)	0.68	5.7 (1.3)	6.6 (4.1)	0.68
SD of overnight glucose (mmol/L)	1.2 (1.1–1.9)	1.1 (0.6–1.4)	0.52	0.7 (0.5–0.9)	0.8 (0.4–2.4)	0.47
Time for which plasma glucose ≤3.5 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–30.0)	0.12	0.0% (0.0–6.1)	0.0% (0.0–24.0)	0.26
Time for which plasma glucose >8.0 mmol/L (%)	20% (0–39)	9.1% (0–83)	0.42	0.0% (0.0–0.0)	0.0% (0.0–62.0)	0.32
LBG1	0.6 (0.1–2.8)	1.6 (0.9–2)	0.13	2.0 (0.6–3.5)	4.6 (0.9–9.1)	0.21
Grade A and B (%)	45% (32–65)	18% (0–58)	0.15	72% (60–100)	9% (2–18)	0.0173
Grade E and F (%)	0.0% (0.0–0.0)	11.9% (0.0–27.2)	0.0100	0.0% (0.0–1.5)	17.7% (9.5–20.5)	0.0493
Insulin infusion (U/h)	1.2 (0.6–1.6)	1.1 (0.5–1.7)	0.89	0.8 (0.5–1.0)	0.8 (0.8–1.0)	0.20
Plasma insulin concentration (pmol/L)	154 (121–314)	197 (121–300)	0.79	195 (143–434)	232 (142–433)	0.25

Data are mean (SD) or median (IQR). Plasma glucose target range was 3.91–8.00 mmol/L. For details of grading system see reference 17. APCam=Artificial Pancreas Project at Cambridge. CL=closed-loop delivery. CSII=continuous subcutaneous insulin infusion. LBG1=low blood-glucose index. *No formal adjustment done for multiple comparisons for secondary comparisons; results should therefore be regarded as hypothesis generating rather than conclusive. †From start of closed-loop control at 20.00 to 08.00. ‡From midnight to 08.00.

Table 3: Secondary comparisons in APCam01 and APCam03

model with those from a generated sample in which patients are rerandomised according to order of closed-loop versus control nights.

During trial planning, all three studies were outlined together, justifying, although not stated in study protocols, a secondary pooled analysis of APCam01 and APCam03. The permutation test took into account that four patients participated in both APCam01 and APCam03. Analyses were done with SAS software (version 9.1) and SPSS (version 15). The Bonferroni method was used for the four primary comparisons,

setting the threshold for significance to 1.25% (5%÷4). No formal adjustment was made for other analyses, which were regarded as secondary and hypothesis-generating.

This trial is registered, number ISRCTN18155883.

Role of the funding source

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

The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From April, 2007, to September, 2008, 19 children and adolescents were enrolled in three studies (figure 3). Two patients participated in three study protocols, six in two, and nine in one. After the first study night, two patients dropped out (figure 3). Table 1 summarises patient characteristics. Data from participants in APCam01 showed that time in the target range for plasma glucose was higher during closed-loop delivery than during standard delivery, but the increase was not significant (table 2). Time lower than the target range was not significantly reduced (table 2). Table 3 shows secondary outcomes for APCam01 and APCam03. Total overnight insulin dose did not differ between treatments. Sensor-based assessments and time concentration profiles are shown in the webappendix (pp 2, 4, 6–8). During closed-loop delivery, variability in plasma glucose decreased from midnight (webappendix pp 6, 8).

Overnight glucose control in APCam02 did not differ after consumption of the two meals (table 4). Time in target range was similar to data recorded in APCam01 during closed-loop delivery. Incremental glucose area-under-the-curve between 18.00 and 22.00 was highest after the rapidly absorbed meal, but this finding was not significant (mean 1021 mmol/L [SD 807] vs -234 mmol/L [481] per 240 min; p=0.08).

Closed-loop delivery after early evening exercise in APCam03 provided the greatest amount of the time spent in the target range of the three studies, but the improvement compared with data for standard treatment was not significant at the corrected level. During continuous infusion one patient presented with plasma glucose lower than 2.0 mmol/L and was given oral glucose (GlucoGel, BBI Healthcare, UK), resulting in study termination for that patient.

Table 5 summarises hypoglycaemic and hyperglycaemic events. All hypoglycaemic events were asymptomatic. During closed-loop delivery, the lowest plasma glucose concentration (3.0 mmol/L) was reported during APCam03 from 02.00 to 02.45, whereas sensor glucose was 4.2 mmol/L or higher. From 21.45 to 22.45, and from 00.15 to 01.30, another patient participating in APCam03 presented with plasma glucose concentrations between 3.1 and 3.3 mmol/L with a value of 3.0 mmol/L at 00.45. Sensor glucose was 4.1 mmol/L or higher. Combining data obtained during all closed-loop studies, 11 (<1%) of 1660 plasma glucose measurements were lower than 3.3 mmol/L, and 24 (>1%) were lower than 3.5 mmol/L. No measurements lower than 3.0 mmol/L were recorded. Combining data obtained during continuous insulin infusion, eight of 992 (<1%) plasma glucose values were lower than 2.5 mmol/L, 32 (3%) were lower than 3.0 mmol/L, 74 (7%) were lower than 3.3 mmol/L, and 108 (11%) were lower than 3.5 mmol/L.

Results of secondary analysis of pooled APCam01 and APCam03 data suggested that closed-loop delivery increased time for which plasma glucose was in the

	Rapidly absorbed evening meal (n=6)	Slowly absorbed evening meal (n=6)	p value*
From start of closed-loop†			
Plasma glucose at start (mmol/L)	11.3 (6.5)	13.1 (5.8)	0.67
Time for which plasma glucose in target range (%)	53% (48–57)	55% (37–64)	0.97
Time for which plasma glucose ≤3.90 mmol/L (%)	0.0% (0.0–3.6)	0.0% (0.0–0.0)	0.16
Overnight glucose (mmol/L)	9.3 (3.1)	8.9 (2.2)	0.83
SD of overnight glucose (mmol/L)	3.0 (1.7–4.5)	2.4 (1.8–3.8)	0.68
Time for which plasma glucose ≤3.5 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–0.0)	0.50
Time for which plasma glucose >8.0 mmol/L (%)	46% (38–52)	45% (36–63)	0.95
LBG1	0.3 (0.0–1.4)	0.2 (0.1–0.3)	0.26
Grade A and B (%)	42% (29–46)	45% (32–77)	0.69
Grade E and F (%)	2.3% (0.0–15.4)	2.2% (0.0–8.9)	0.87
Insulin infusion (U/h)	1.7 (1.2–1.8)	1.4 (0.8–1.9)	0.46
Plasma insulin concentration (pmol/L)	250 (157–415)	222 (185–540)	0.60
After midnight‡			
Time for which plasma glucose in target range (%)	86% (47–91)	83% (33–100)	0.98
Time for which plasma glucose ≤3.90 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–0.0)	0.50
Overnight glucose (mmol/L)	7.4 (1.7)	7.4 (1.9)	>0.99
SD of overnight glucose (mmol/L)	1.4 (1.1–1.8)	1.4 (0.9–2.1)	0.92
Time for which plasma glucose ≤3.5 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–0.0)	0.50
Time for which plasma glucose >8.0 mmol/L (%)	14% (6.1–53.0)	17% (0–67)	0.97
LBG1	0.4 (0.0–1.0)	0.4 (0.2–0.6)	0.50
Grade A and B (%)	55% (35–68)	72% (23–88)	0.71
Grade E and F (%)	0.0% (0.0–2.4)	0.0% (0.0–6.6)	>0.99
Insulin infusion (U/h)	1.1 (0.9–1.7)	1.2 (0.8–1.3)	0.77
Plasma insulin concentration (pmol/L)	129 (111–250)	117 (101–415)	0.44

Data are mean (SD) or median (IQR). Plasma glucose target range was 3.91–8.00 mmol/L. For details of grading system see reference 17. LBG1=low blood-glucose index. APCam=Artificial Pancreas Project at Cambridge. *No formal adjustment for multiple comparisons was done for secondary comparisons. †From the start of closed-loop control at 18.30 to 08.00. ‡From midnight to 08.00.

Table 4: Comparisons in APCam02

	APCam01 (n=12)		APCam02 (n=6)		APCam03 (n=9)		All studies	
	CL	CSII	CL-RA*	CL-SA*	CL†	CSII	CL	CSII
Plasma glucose ≤2.0 mmol/L								
Any	1	..	1
<30 min	1‡	..	1‡
Plasma glucose 2.1–2.5 mmol/L								
Any	..	1	1	..	2
<30 min
30–60 min	..	1	1
60–90 min	1	..	1
Plasma glucose >2.5 to 3.0 mmol/L								
Any	..	3	1§	3	1§	6
<30 min	..	1	1	..	2
30–60 min	..	1	1§	2	1§	3
60–240 min
240–360 min	..	1	1

(Continues on next page)

target range and reduced time lower than the target range (table 2). A more apparent improvement in time within target was recorded after midnight, when closed-loop delivery became fully effective (table 6). At low and high glucose concentrations, closed-loop control consistently outperformed continuous infusion (figure 4). Pooled data from all closed-loop studies showed that plasma glucose was lower than the target range for 4% of the time, within target for 61%, and higher for 35%. Time in target increased to 75% for data obtained after midnight, which was when closed-loop control became fully effective.

Discussion

Our results show that overnight manual closed-loop insulin delivery can improve glucose control and reduce risk of hypoglycaemia in young patients with type 1 diabetes. Secondary analysis of pooled data showed that time for which plasma glucose concentration was in the target range increased and frequency of low plasma glucose concentrations was reduced during closed-loop control. For data obtained after midnight, time spent in the target range more than doubled during closed loop compared with continuous infusion. Average overnight insulin delivery was similar during closed-loop delivery and standard treatment.

Closed-loop systems could transform management of type 1 diabetes, but their introduction is likely to be gradual, starting from straightforward applications such as shutting off of the pump at low glucose concentrations¹⁹ or overnight closed-loop delivery, proceeding to more complex applications providing 24-h control. Overnight closed-loop delivery is appealing because it addresses the issue of nocturnal hypoglycaemia. On standard insulin regimens, 45–60% of young people can have profound, severe, persistent, and generally asymptomatic hypoglycaemia overnight.²⁰ Ability to recognise hypoglycaemia is difficult for children with type 1 diabetes and their parents. For children, poor ability to detect low blood glucose concentrations could be a substantial and underappreciated risk factor for severe hypoglycaemia.²¹ Prevention of hypoglycaemia overnight could also improve daytime glucose control.

Transiently high or persistently raised postprandial glucose concentrations can lead to insulin stacking and overdosing, resulting in late postprandial hyperinsulinaemia and subsequent hypoglycaemia, as reported with some closed-loop algorithms.²² In our studies, postprandial glucose concentrations were increased after large evening meals, but overall glucose control was unaffected and risk of hypoglycaemia was low, documenting effective, non-aggressive insulin delivery. Moderate-intensity late-afternoon or early-evening exercise in young people is a frequent occurrence and increases glucose requirements in the early morning, exacerbating risk of nocturnal hypoglycaemia.²³ Our closed-loop algorithm ameliorated this risk and maintained good glucose control.

	APCam01 (n=12)		APCam02 (n=6)		APCam03 (n=9)		All studies	
	CL	CSII	CL-RA*	CL-SA*	CL†	CSII	CL	CSII
(Continued from previous page)								
Plasma glucose ≥ 16.7 mmol/L								
Any	1 (1)	1 (1)	2 (1)	2 (2)	..	3 (2)	5 (4)	4 (3)
<30 min	1 (0)	..	1
30–60 min	1 (1)	1 (1)	..
60–120 min	1 (0)	1 (1)	2 (1)	..
120–180 min	1 (1)	..	1 (1)	1 (1)	1 (1)
180–240 min
240–360 min	..	1 (1)	1 (1)	1 (1)	1 (1)	2 (2)

Data in parentheses are number of occasions for which study started with plasma glucose 16.7 mmol/L or higher. After start of study (20.00 for APCam01 and APCam03, 18.30 for APCam03), all hypoglycaemic events were asymptomatic and, apart from for one patient‡, no treatment was given. All hypoglycaemic events at 3.0 mmol/L or less occurred at or after midnight. APCam=Artificial Pancreas Project at Cambridge. CL=closed-loop delivery. CSII=continuous subcutaneous insulin infusion. *Closed-loop delivery after rapidly (RA) or slowly (SA) absorbed evening meal. †During closed-loop delivery in APCam03, two patients presented with hypoglycaemia during exercise with plasma glucose concentration lower than 3 mmol/L and were given 15 g carbohydrate. ‡Study stopped at 04.00 when plasma glucose was lower than 2.0 mmol/L and oral glucose was consumed; duration of hypoglycaemia could not be established. §Three consecutive plasma glucose values at 3.0 mmol/L.

Table 5: Frequency and duration of hypoglycaemia and hyperglycaemia during closed-loop delivery and continuous subcutaneous insulin infusion

	CL (n=21)	CSII (n=21)	p value*
From start of closed-loop†			
Overnight glucose (mmol/L)	7.0 (1.8)	8.1 (3.6)	0.29
SD of overnight glucose (mmol/L)	1.6 (1.1–2.8)	2.4 (1.7–3.2)	0.19
Time for which plasma glucose ≤ 3.5 mmol/L (%)	0.0% (0.0–4.1)	0.0% (0.0–23)	0.0237
Time for which plasma glucose > 8.0 mmol/L (%)	25% (0.0–45.0)	35% (18–61)	0.13
LBGI	1.1 (0.1–2.7)	1.6 (0.1–6.6)	0.0330
Grade A and B (%)	51% (34–74)	26% (10–38)	0.0061
Grade E and F (%)	0.0% (0.0–5.2)	11.8% (0.1–40.9)	0.0049
Insulin infusion (U/h)	1.0 (0.6–1.4)	0.9 (0.6–1.6)	0.58
Plasma insulin concentration (pmol/L)	199 (148–405)	233 (146–383)	0.23
After midnight‡			
Time for which plasma glucose in target range (%)	79% (64–97)	35% (3.0–64)	0.0025
Time for which plasma glucose ≤ 3.90 mmol/L (%)	3.0% (0.0–12.0)	6.1% (0.0–61.0)	0.0277
Overnight glucose (mmol/L)	6.3 (1.6)	7.0 (3.8)	0.51
SD of overnight glucose (mmol/L)	1.1 (0.7–1.6)	1.1 (0.5–1.6)	0.83
Time for which plasma glucose ≤ 3.5 mmol/L (%)	0.0% (0.0–0.0)	0.0% (0.0–27.0)	0.0292
Time for which plasma glucose > 8.0 mmol/L (%)	0.0% (0.0–24.0)	3.0% (0.0–66.0)	0.18
LBGI	1.0 (0.1–3.1)	2.4 (0.1–9.1)	0.0347
Grade A and B (%)	60% (39–78)	10% (0–46)	0.0067
Grade E and F (%)	0.0% (0.0–0.0)	16.8% (0.0–23.9)	0.0008
Insulin infusion (U/h)	0.9 (0.6–1.4)	0.9 (0.6–1.6)	0.52
Plasma insulin concentration (pmol/L)	173 (125–363)	200 (142–337)	0.23

Data are mean (SD) or median (IQR). Plasma glucose target range was 3.91–8.00 mmol/L. Time in target and time below target from start of closed-loop delivery are shown in table 2. For details of grading system see reference 17. CL=closed-loop delivery. n=number of nights per treatment. CSII=continuous subcutaneous insulin infusion. LBGI=low blood-glucose index. APCam=Artificial Pancreas Project at Cambridge. *No formal adjustment for multiple comparisons was done for secondary comparisons; results should therefore be regarded as hypothesis-generating rather than conclusive. †From start of closed-loop control at 20.00 to 08.00. ‡From midnight to 08.00. §APCam02 did not provide CSII data.

Table 6: Comparisons between closed-loop delivery and continuous subcutaneous insulin infusion after pooling APCam01 and APCam03 data§

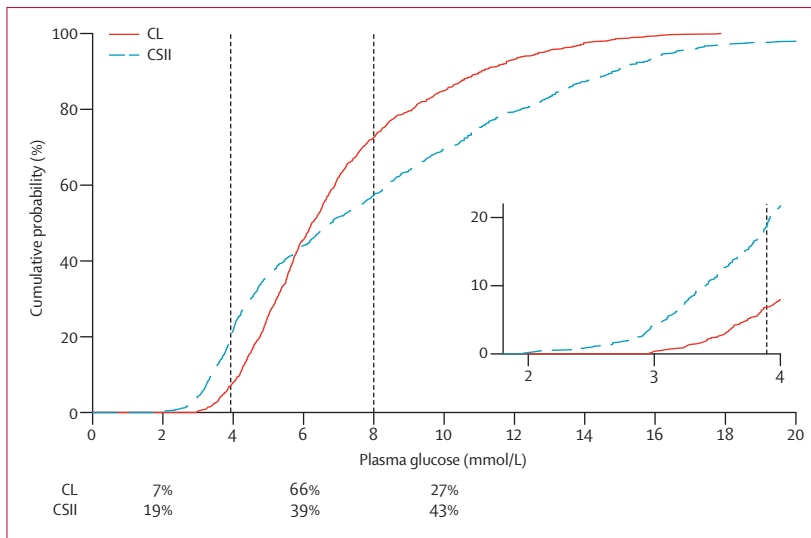


Figure 4: Cumulative probability of plasma glucose concentrations during closed-loop insulin delivery and continuous subcutaneous insulin infusion

Data obtained during APCam01 and 03 (APCam02 did not provide continuous subcutaneous insulin infusion [CSII] data). Vertical dashed lines denote target glucose range (3.91–8.00 mmol/L). Inset shows detail at low plasma glucose concentrations. Numbers below are total percentage time for which plasma glucose was lower than, within, or higher than the target range from the start of closed-loop control at 20.00 until 08.00 the next day. APCam=Artificial Pancreas Project at Cambridge. CL=closed-loop delivery.

Apart from during continuous infusion in one patient, we did not give supplemental carbohydrates or insulin. Real-time alarms or predictive alarms could be used to avoid or reverse low glucose concentrations.²⁴ To detect the two most pronounced hypoglycaemia events reported during our closed-loop studies, a high sensor alarm threshold of 4.2 mmol/L would be needed. Patients sleep through 70% of individual alarms and 35% of repeated alarm events,²⁵ possibly because of alarm fatigue induced by a high frequency of false-positive alarms. Alarm-based hypoglycaemia detection and prevention is therefore of limited reliability, but could further reduce hypoglycaemia risk during overnight closed-loop delivery.

Using Medtronic's closed-loop system of external physiological insulin delivery,²² Weinzimer and colleagues²⁶ assessed a proportional-integral-derivative control algorithm and Guardian Real-Time in 17 adolescents and showed excellent control and feasibility of a hybrid closed-loop system during day and night. Three hypoglycaemic events at venous glucose concentrations of 3.3 mmol/L or lower were recorded and treated, all between 23.00 and 01.00. Schaller and co-workers²⁷ investigated closed-loop delivery during fasting conditions in adults. However, no studies have compared closed-loop delivery and continuous subcutaneous insulin infusion, or assessed the effect of large evening meals or exercise.

Insulin requirements vary greatly between individuals, and to a lesser degree diurnally and from day to day.²⁸ Our control algorithm coped with these variations effectively by initialising individual insulin sensitivity

from patients' total daily insulin dose and usual basal insulin requirements and then adapting this estimate in real time on the basis of administered insulin and resulting sensor glucose concentrations. The adaptive nature of the control algorithm resulted in safe and effective insulin dosing.

Sensing errors have been perceived as the main obstacle to safe and efficacious closed-loop glucose control.^{29,30} In our studies, the sensors did well, although we registered temporal losses of accuracy that were attributable to sensor artifacts and persistent deviations caused by calibration errors. During closed-loop delivery, sensing errors reduced time in target by 10–15%, but average plasma and sensor glucose concentrations were almost identical. Advancements in glucose-sensing technologies could further improve performance of closed-loop systems. Fully automated closed-loop delivery will need wireless data transmission to replace manual control of the pump by nurses. These technological steps are important but routine and should not affect closed-loop performance.

Contributors

RH coordinated the studies. DBD, RH, CLA, MEW, and LJC codedigned the studies. JMA, CLA, and DE were responsible for patient screening and enrolment. JMA and DE requested informed consent from the patients or their parents. JMA, DE, JH, and ADP provided patient care, obtained the clinical and laboratory data and contributed to biochemical analysis. LJC and MEW carried out randomisation. MEW, DX, MN, RH, TH, AML, LJC, and CK carried out or supported the data analysis including the statistical analyses. RH designed and implemented the glucose controller. RH, DBD, MEW, and CLA contributed to the interpretation of the results and the writing and critical review of the report. All authors have seen and approved the final version of the report.

Conflicts of interest

RH has been paid lecture fees by Minimed Medtronic, Abbott Diabetes Care, Lifescan, Novo Nordisk, and BBraun. RH reports two patent applications. CLA has received lecture fees from Novo Nordisk. CK has served as a consultant to Medtronic International Trading Sàrl. JMA, CLA, LJC, DE, JH, DX, TH, AMFL, MN, ADP, MEW, and DBD declare that they have no competing financial interests.

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References

- 1 LaPorte R, Matsushima M, Chang Y. Prevalence and incidence of insulin-dependent diabetes. In: National Diabetes Data Group, ed. *Diabetes in America*, 2nd edn. Bethesda, MD: National Institutes of Health, 1995: 37–46.
- 2 EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 2000; 355: 873–76.

- 3 White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001; **139**: 804–12.
- 4 Bulsara MK, Holman CD, Davis EA, Jones TW. The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. *Diabetes Care* 2004; **27**: 2293–98.
- 5 Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care* 2005; **28**: 1231–39.
- 6 Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; **359**: 1464–76.
- 7 Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J* 1978; **1**: 204–07.
- 8 Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med* 2006; **23**: 1–12.
- 9 Steil GM, Rebrin K. Closed-loop insulin delivery—what lies between where we are and where we are going? *Expert Opin Drug Deliv* 2005; **2**: 353–62.
- 10 Renard E, Costalat G, Chevassus H, Bringer J. Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metab* 2006; **32**: 497–502.
- 11 Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technol Ther* 2005; **7**: 28–47.
- 12 Brage S, Ekelund U, Brage N, et al. Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. *J Appl Physiol* 2007; **103**: 682–92.
- 13 Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008; **31**: 1160–64.
- 14 Hovorka R, Shojaee-Moradie F, Carroll PV, et al. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am J Physiol* 2002; **282**: E992–1007.
- 15 Mazor E, Averbuch A, Bar-Shalom Y, Dayan J. Interacting multiple model methods in target tracking: a survey. *IEEE Trans Aerosp Electron Syst* 1998; **34**: 103–23.
- 16 Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. *Diabetes Care* 1998; **21**: 1870–75.
- 17 Chassin LJ, Wilinska ME, Hovorka R. Grading system to assess clinical performance of closed-loop glucose control. *Diabetes Technol Ther* 2005; **7**: 72–82.
- 18 Good PI. Permutation, parametric and bootstrap tests of hypotheses, 3rd edn. New York: Springer, 2005.
- 19 Buckingham B, Cobry E, Clinton P, et al. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Ther* 2009; **11**: 93–97.
- 20 Porter PA, Keating B, Byrne G, Jones TW. Incidence and predictive criteria of nocturnal hypoglycemia in young children with insulin-dependent diabetes mellitus. *J Pediatr* 1997; **130**: 366–72.
- 21 Gonder-Frederick L, Zrebiec J, Bauchowitz A, et al. Detection of hypoglycemia by children with type 1 diabetes 6 to 11 years of age and their parents: a field study. *Pediatrics* 2008; **121**: e489–495.
- 22 Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes* 2006; **55**: 3344–50.
- 23 McMahon SK, Ferreira LD, Ratnam N, et al. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. *J Clin Endocrinol Metab* 2007; **92**: 963–8.
- 24 McGarraugh G, Bergenstal R. Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator continuous glucose monitoring system. *Diabetes Technol Ther* 2009; **11**: 145–50.
- 25 Buckingham B, Block J, Burdick J, et al. Response to nocturnal alarms using a real-time glucose sensor. *Diabetes Technol Ther* 2005; **7**: 440–47.
- 26 Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care* 2008; **31**: 934–39.
- 27 Schaller HC, Schaupp L, Bodenlenz M, et al. On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with type 1 diabetes. *Diabet Med* 2006; **23**: 90–93.
- 28 Williams RM, Dunger DB. Insulin treatment in children and adolescents. *Acta Paediatr* 2004; **93**: 440–46.
- 29 Hovorka R, Wilinska ME, Chassin LJ, Dunger DB. Roadmap to the artificial pancreas. *Diabetes Res Clin Pract* 2006; **74** (suppl 2): S178–82.
- 30 Wilinska ME, Budiman ES, Taub MB, et al. Overnight closed-loop insulin delivery with model predictive control: assessment of hypoglycemia and hyperglycemia risk using simulation studies. *J Diabetes Sci Technol* 2009; **3**: 1109–20.