

Safety, efficacy and glucose turnover of reduced prandial boluses during closed-loop therapy in adolescents with type 1 diabetes: a randomized clinical trial

D. Elleri^{1,2}, M. Biagioni^{1,2}, J. M. Allen^{1,2}, K. Kumareswaran², L. Leelarathna², K. Caldwell², M. Nodale², M. E. Wilinska^{1,2}, A. Haidar², P. Calhoun³, C. Kollman³, N. C. Jackson⁴, A. M. Umpleby⁴, C. L. Acerini^{1,2}, D. B. Dunger^{1,2} & R. Hovorka^{1,2}

¹ Department of Paediatrics, University of Cambridge, Cambridge, UK

² Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK

³ The Jaeb Center for Health Research, Tampa, FL, USA

⁴ Diabetes and Metabolic Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Aims: To evaluate safety, efficacy and glucose turnover during closed-loop with meal announcement using reduced prandial insulin boluses in adolescents with type 1 diabetes (T1D).

Methods: We conducted a randomized crossover study comparing closed-loop therapy with standard prandial insulin boluses versus closed-loop therapy with prandial boluses reduced by 25%. Eight adolescents with T1D [3 males; mean (standard deviation) age 15.9 (1.5) years, glycated haemoglobin 74 (17) mmol/mol; median (interquartile range) total daily dose 0.9 (0.7, 1.1) IU/kg/day] were studied on two 36-h-long visits. In random order, subjects received closed-loop therapy with either standard or reduced insulin boluses administered with main meals (50–80 g carbohydrates) but not with snacks (15–30 g carbohydrates). Stable-label tracer dilution methodology measured total glucose appearance (Ra_{total}) and glucose disposal (Rd).

Results: The median (interquartile range) time spent in target (3.9–10 mmol/l) was similar between the two interventions [74 (66, 84)% vs 80 (65, 96)%; $p = 0.87$] as was time spent above 10 mmol/l [21.8 (16.3, 33.5)% vs 18.0 (4.1, 34.2)%; $p = 0.87$] and below 3.9 mmol/l [0 (0, 1.5)% vs 0 (0, 1.8)%; $p = 0.88$]. Mean plasma glucose was identical during the two interventions [8.4 (0.9) mmol/l; $p = 0.98$]. Hypoglycaemia occurred once 1.5 h post-meal during closed-loop therapy with standard bolus. Overall insulin delivery was lower with reduced prandial boluses [61.9 (55.2, 75.0) vs 72.5 (63.6, 80.3) IU; $p = 0.01$] and resulted in lower mean plasma insulin concentration [186 (171, 260) vs 252 (198, 336) pmol/l; $p = 0.002$]. Lower plasma insulin was also documented overnight [160 (136, 192) vs 191 (133, 252) pmol/l; $p = 0.01$, pooled nights]. Ra_{total} was similar [26.3 (21.9, 28.0) vs 25.4 (21.0, 29.2) μ mol/kg/min; $p = 0.19$] during the two interventions as was Rd [25.8 (21.0, 26.9) vs 25.2 (21.2, 28.8) μ mol/kg/min; $p = 0.46$].

Conclusions: A 25% reduction in prandial boluses during closed-loop therapy maintains similar glucose control in adolescents with T1D whilst lowering overall plasma insulin levels. It remains unclear whether closed-loop therapy with a 25% reduction in prandial boluses would prevent postprandial hypoglycaemia.

Keywords: closed-loop insulin delivery, postprandial hypoglycaemia, type 1 diabetes

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Introduction

The treatment goal of type 1 diabetes (T1D) is to maintain tight glycaemic control whilst minimizing the risk of hypoglycaemia [1], but this is particularly challenging during adolescence [2]. The Diabetes Control and Complications Trial showed that, even when intensified insulin treatment was rigorously applied, glycated haemoglobin (HbA1c) levels were higher in adolescents compared with adults [3]. Data from the T1D Exchange document that only 20% of young people aged 13–20 years meet HbA1c targets set by the American Diabetes Association

and the International Society for Pediatric and Adolescent Diabetes [4]. The psychological and social aspects associated with adolescence often lead to worsening of metabolic control exacerbated by increased insulin requirements related to the physiological changes of puberty.

Closed-loop therapy is an emerging treatment method for T1D [5], adopting glucose-responsive insulin delivery directed by a control algorithm according to real-time sensor glucose levels. The efficacy and safety of closed-loop therapy in adolescents have been demonstrated in multiple short-term clinical trials, mainly in laboratory conditions, and more recently in the outpatient and home settings by us and others [6–10]. In our studies, between-meal insulin delivery is automated and modulated by the algorithm, whereas prandial insulin boluses are administered manually using a bolus calculator as per standard clinical practice. Compared with conventional insulin pump therapy, this so-called closed-loop with meal announcement improves the time spent in normoglycaemia whilst reducing

Correspondence to: Daniela Elleri, Department of Paediatrics, Addenbrooke's Hospital, University of Cambridge, Level 8, Box 116, Hills Rd, Cambridge CB2 0QQ, UK.
E-mail: de250@medschl.cam.ac.uk

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the risk of hypoglycaemia in children and adolescents as well as in adults and pregnant women with T1D [6,7,11,12]. These outcomes were also observed in a group of adolescents over a 36-h period in the clinical research facility [13]; overnight closed-loop insulin delivery was found to be particularly beneficial, whilst the achievement of optimum glucose levels in the daytime was complicated by the rapid glucose fluctuations associated with meals and physical activity. Four out of nine episodes of hypoglycaemia occurred in the postprandial period and probably resulted from a high prandial insulin dose.

It is currently unknown if reducing prandial insulin boluses provides a similar level of control during closed-loop therapy whilst limiting postprandial hyperinsulinaemia and reducing risk of post-meal hypoglycaemia. We tested this hypothesis in the present study and additionally employed a stable-label glucose methodology to measure glucose turnover to determine the effect of reduced prandial insulin on glucose turnover.

Materials and Methods

Subjects and Study Protocol

The study was conducted at the Wellcome Trust Clinical Research Facility at Addenbrooke's Hospital, Cambridge, UK, and was registered with clinicaltrials.gov (identifier NCT01629251).

Young people aged 12–18 years with T1D on insulin pump therapy were recruited through three paediatric diabetes clinics at Cambridge University Hospital, University College Hospital London and Norwich Hospital. The inclusion criteria were T1D (World Health Organization criteria), diabetes duration of at least 1 year and insulin pump therapy for at least 3 months. Adolescents with poor glycaemic control [$\text{HbA}_{1c} > 12\%$ (108 mmol/mol)], insulin resistance (total daily dose $> 2 \text{ IU/kg/day}$) and clinically significant nephropathy or retinopathy were excluded.

The study adopted an open-label randomized crossover design. Participants received closed-loop insulin delivery between meals, combined with manually administered prandial boluses. In random order, standard meal insulin boluses or reduced meal insulin boluses during two 36-h study visits, 1–6 weeks apart, were applied.

Prandial insulin boluses administered with each main meal were calculated by bolus calculator with insulin-to-carbohydrate ratios and insulin sensitivity factors being determined by treating clinicians. On one occasion (closed-loop therapy with standard meal insulin boluses), the standard bolus was given at each meal, whereas on the other occasion (closed-loop therapy with reduced meal insulin boluses), the bolus at each meal was reduced by 25%.

On each occasion, participants attended the clinical research facility from 17:30 hours on day 1 until 08:00 hours on day 3. Continuous glucose monitoring (FreeStyle Navigator[®], Abbott Diabetes Care, Alameda, CA, USA) was established 24–48 h before each study visit by inserting a single sensor. During the study visit, the participants' insulin pump was replaced by a study pump (Animas[®] 2020, Animas Corp., West Chester, PA, USA). The subjects consumed self-selected meals and snacks from standardized menus that were identical on the two study

visits. They consumed an evening meal (80 g carbohydrates) at 19:00 hours, breakfast (50 g carbohydrates) at 08:00 hours and lunch (70 g carbohydrates) at 13:00. Snacks containing 15 g carbohydrates were given in the evening at 21:00 hours on day 1 and day 2 and in the morning at 10:15 hours on day 2. An afternoon snack of 30 g carbohydrates was consumed at 16:00 hours on day 2. No insulin boluses were given with snacks. Subjects engaged in physical activity on a stationary bicycle for two separate 20-min sessions at 10:40 and 17:30 hours on day 2.

Closed-loop System

An algorithm based on model-predictive control [6] was used to adjust basal insulin delivery based on glucose sensor readings at 15-min intervals from 19:30 hours on day 1 until 08:00 hours on day 3 for $\sim 32 \text{ h}$, as previously described [6,13]. A model predictive algorithm version 0.3.14 was used.

Glucose Turnover

A stable-label glucose tracer was infused in a time-variant fashion to mimic the expected total appearance of glucose [14]. At 06:00 hours, a primed (4 mg/kg over 1 min) $[6,6\text{-}^2\text{H}_2]$ glucose infusion (Cambridge Isotope Laboratories, Andover, MA, USA) was started and continued at a fixed rate of 0.04 mg/kg/min until 08:00 hours. From 08:00 hours until midnight the infusion of $[6,6\text{-}^2\text{H}_2]$ glucose continued at a variable rate to mimic the expected total systemic glucose appearance (sum of endogenous glucose production and meal attributable total glucose appearance; R_{a_total}) in post-meal conditions and to reduce variations in the tracer-to-tracee ratio [15]. The infusion rate was varied at 15-min intervals, as shown in Table S1. These infusion rates were derived from previous studies on glucose absorption patterns of meals with different glycaemic loads in young people with T1D [16].

Tracer-to-tracee ratios of $[6,6\text{-}2\text{H}_2]$ glucose were calculated using ions mass/charge ratio (m/z) $M + 0$ and $M + 2$, based on a method described previously [17]. The glucose turnover calculations were based on the maximum likelihood method [18], modified for a Bayesian implementation in WinBUGS (MRC Biostatistics Unit, Cambridge, UK) version 1.4.3. R_{a_total} represents total glucose appearance corresponding to the sum of all meal-derived glucose (breakdown of sugars and complex carbohydrates) and endogenous glucose production [16]. R_{a_total} and glucose disposal (R_d) were calculated for 24 h from 08:00 hours on day 2 until 08:00 hours on day 3. Peripheral insulin sensitivity was calculated as the incremental area under the R_d curve above fasting divided by the incremental plasma insulin concentration above fasting [19,20]. The metabolic clearance of insulin was calculated as the incremental insulin delivery above fasting divided by the incremental plasma insulin concentration above fasting.

Sampling and Assay

Blood samples were taken to measure plasma glucose and insulin levels every 15 (postprandial period) to 60 (overnight) min. Plasma glucose was measured using a YSI2300 STAT Plus analyser (YSI, Farnborough, UK) and plasma insulin by immunochemiluminometric assay (Invitron, Monmouth,

Table 1. Study outcomes based on plasma glucose between 24:00 hours on day 1 until 08:00 hours on day 3 (32 h) is considered for analysis during closed-loop therapy with standard prandial insulin boluses and closed-loop therapy with reduced prandial insulin boluses.

	Closed-loop with standard prandial boluses (n = 8)	Closed-loop with reduced prandial boluses (n = 8)	p
Primary outcome			
Median (IQR) percentage of time spent in target of 3.9–10 mmol/l	80 (65, 96)	74 (66, 84)	0.87
Secondary outcomes			
Mean (s.d.) glucose, mmol/l	8.4 (0.9)	8.4 (0.9)	0.98
Median (IQR) standard deviation of glucose, mmol/l	1.9 (1.4, 2.3)	2.1 (1.8, 2.5)	0.40
Median (IQR) percentage of time spent in target of 3.9–8 mmol/l	48 (30, 54)	42 (36, 52)	0.84
<i>Hypoglycaemia: median (IQR), %</i>			
≤3.9 mmol/l (%)	0.0 (0.0, 1.8)	0.0 (0.0, 1.5)	0.88
≤3.5 mmol/l (%)	0.0 (0.0, 0.9)	0.0 (0.0, 0.9)	0.88
Median (IQR) low blood glucose index, unitless	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	0.93
<i>Hyperglycaemia: median (IQR), %</i>			
>10 mmol/l	18.0 (4.1, 34.2)	21.8 (16.3, 33.5)	0.87
>16.6 mmol/l	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	—*
Median (IQR) insulin infusion, IU/h	1.5 (1.3, 1.6)	1.4 (1.2, 1.7)	0.20
Median (IQR) insulin concentration, pmol/l†	252 (198, 336)	186 (171, 260)	0.002
Median (IQR) insulin boluses, IU	25.7 (24.1, 29.4)	18.6 (17.6, 21.4)	<0.001
Median (IQR) total insulin, IU	72.5 (63.6, 80.3)	61.9 (55.2, 75.0)	0.01

IQR, interquartile range; s.d., standard deviation.

*No subject had values >16.6 mmol/l on either visit.

†One subject was excluded as a result of having a much greater insulin concentration on both visits.

UK). Venous blood samples for determination of background glucose isotope enrichment were taken at 05:50, 05:55 and 06:00 hours. Samples for the determination of enriched glucose and plasma glucose were taken at 07:45, 07:55 and 08:00 hours and then every 15–30 min throughout the study, except from midnight to 08:00 hours, when samples were taken hourly. Isotope ratios of [$6,6^2\text{H}_2$]glucose were measured by gas chromatography-mass spectrometry on an Agilent GCMS 5975C MSD (Agilent Technologies, Santa Clara, CA, USA) using selected ion monitoring of a penta-O-trimethylsilyl-D-glucose-O-methyloxime derivative to measure ions mass/charge ratio (m/z) 319.2 (M + 0) and 321.2 (M + 2) [17].

Statistical Analysis

The primary outcome was time spent with plasma glucose in the target range (3.9–10 mmol/l) between 24:00 hours on day 1 and 08:00 hours on day 3 (32 h). Secondary outcomes included mean glucose, time spent with plasma glucose in the hypoglycaemia range (≤3.9 and ≤3.5 mmol/l), low blood glucose index, time spent with plasma glucose in the hyperglycemia range (>10 and >16.6 mmol/l), and insulin-related metrics between 24:00 hours on day 1 and 08:00 hours on day 3 (32 h). A repeated-measures regression model was fit to compare the two treatments adjusting for period effect and based on the ranked normal transformation (except for mean glucose, which was not transformed because it already had an approximate normal distribution). Statistical analyses were performed using SAS 9.4. All p values are two-tailed and values <0.05 were considered to indicate statistical significance. Results are presented as median (interquartile range) or mean (s.d.) unless stated otherwise.

Results

Participants

A flowchart of participants through the study is shown in Figure S1. We studied eight adolescents (three males) aged 15.9 (1.5) years, BMI 24 (3) kg/m², HbA1c [8.9 (1.6)% or 74 (17) mmol/mol], diabetes duration 7 (2) years, on insulin pump therapy for 4 (2) years, and total daily insulin dose 59 (40, 83) IU/day [0.9 (0.7, 1.1) IU/kg/day].

Closed-loop Glucose Control

The time spent with plasma glucose levels within the target range of 3.9–10 mmol/l (the primary outcome) was similar between the two interventions (Table 1 and Figure 1). This outcome was similar when evaluated based on sensor glucose (Table S3). Hypoglycaemia occurred once 1.5 h after a meal during closed-loop with standard prandial boluses. Total insulin delivery and plasma insulin were lower with reduced prandial insulin boluses. Insulin infusion rates were similar between the two interventions in the two overnight periods. Plasma insulin levels, however, were lower overnight with reduced plasma insulin boluses [first night: 137 (106, 192) vs 172 (126, 256) pmol/l; p = 0.01; second night: 161 (148, 234) vs 196 (159, 252) pmol/l; p = 0.09; pooled nights: 160 (136, 192) vs 191 (133, 252) pmol/l; p = 0.01], as shown in Figure 3. Study outcomes during day-time and night-time are also shown in Table S4.

Glucose Turnover

Both Ra_{total} and Rd were similar on the two occasions (Figure 2). Insulin sensitivity and plasma insulin clearance

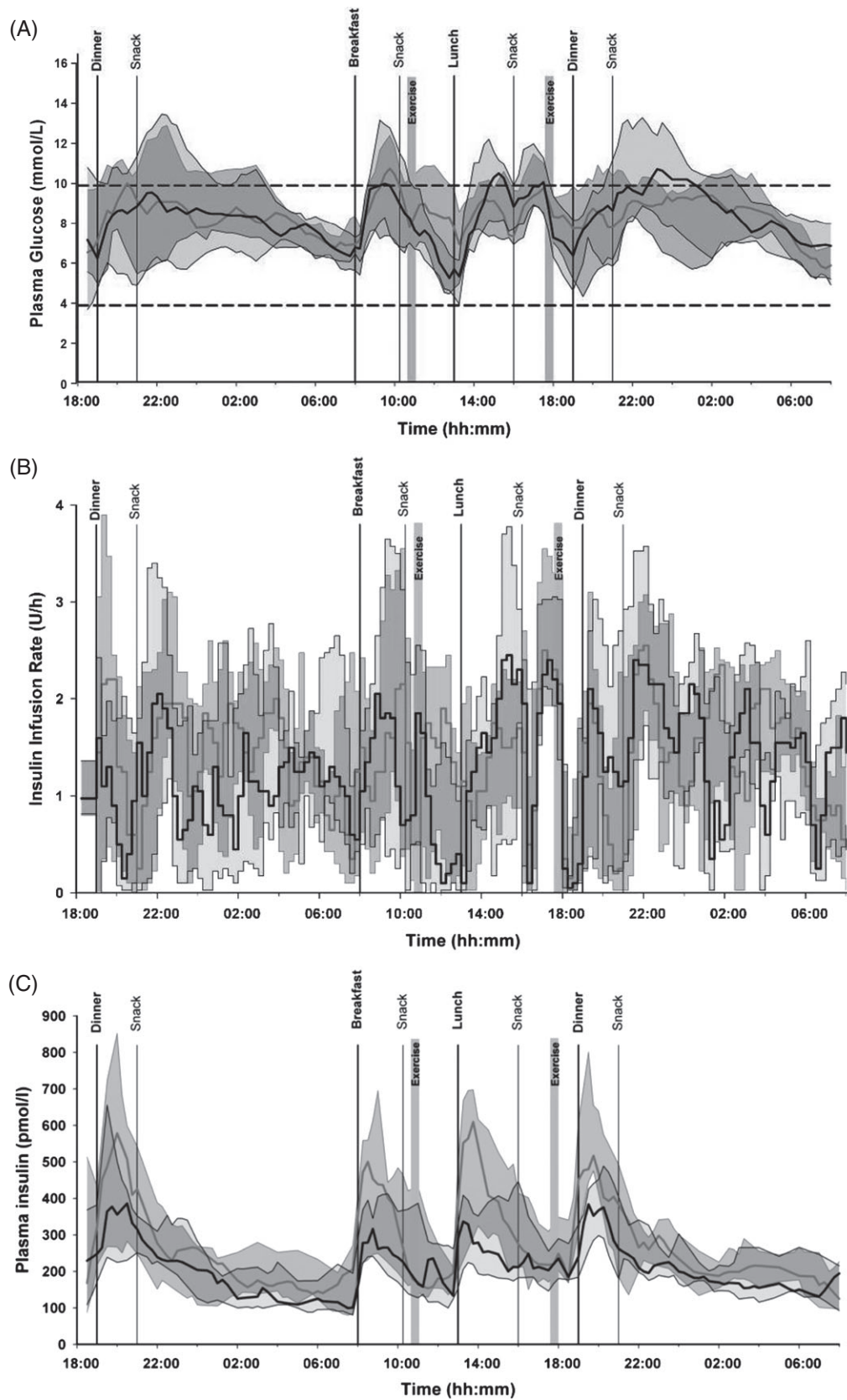


Figure 1. Plasma glucose concentration (A), basal insulin infusion rates (B) and the plasma insulin levels (C) during closed-loop therapy with standard prandial insulin boluses (grey line) and closed-loop therapy with reduced prandial boluses (black line). Values are median, interquartile ranges.

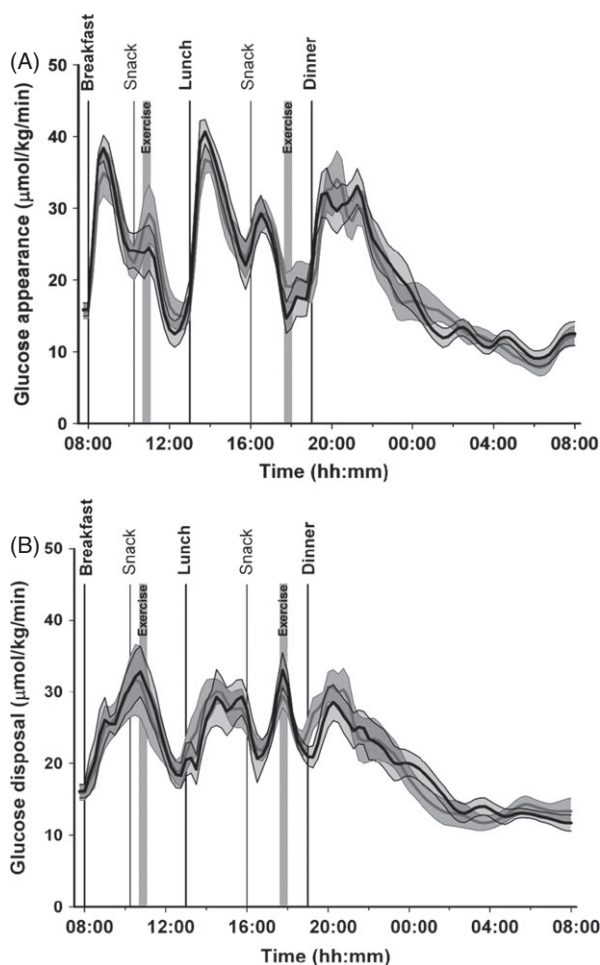


Figure 2. (A) Total glucose appearance and (B) disposal (mean, standard error) from 08:00 hours on day 2 for 24 h during closed-loop therapy with standard prandial boluses (grey line) and closed-loop with reduced prandial boluses (black line).

were also similar (Table 2). Similarly, no difference in glucose turnover between treatments was found when the overnight period was considered (Table S2).

Continuous Glucose Monitoring

The accuracy of sensor glucose measurements was calculated as compared with plasma glucose data measured by YSI2300 STAT Plus analyser. Each YSI glucose measurement was paired

with an interpolated sensor value only if this existed within ± 6 min of the YSI glucose measurement. This approach is similar to that used to calculate sensor accuracy in previous clinical studies. The median absolute relative difference of Navigator CGM was 7.5% and the mean absolute relative difference was 9.7%.

Discussion

In the present study we showed that closed-loop insulin delivery coupled with a 25% reduction in prandial insulin achieves similar glucose control compared with closed-loop with standard boluses in a group of adolescents with T1D. The time spent with plasma glucose levels within the target range of 3.9–10 mmol/l was 74% when prandial boluses were reduced and 80% with standard boluses ($p = 0.87$). Mean plasma glucose levels were identical [8.4 (0.9) mmol/l, reduced vs standard bolus; $p = 0.98$].

Closed-loop insulin delivery is particularly efficacious when coupled with manual prandial insulin boluses to offset delays associated with absorption of subcutaneous insulin and glucose sensing. Weinzimer et al. [21] observed that postprandial glucose control improved when priming insulin bolus was given with meals during closed-loop using a proportional-integral-derivate algorithm. El-Khatib et al. [22] demonstrated improved postprandial control with adaptive meal priming boluses compared with a scheme avoiding meal boluses during a bi-hormonal closed-loop in adolescents and adults. Haidar et al. [23] showed that carbohydrate-matching insulin bolus improved post-breakfast glycaemic control as compared with weight-dependent bolus during bi-hormonal closed-loop in adults.

The calculation of prandial insulin based on the amount of carbohydrates (carbohydrate counting) is commonly promoted by educational interventions [24]. Insulin pumps are equipped with in-built bolus calculators employing premeal glucose levels and insulin on board. Combining carbohydrate counting with closed-loop insulin delivery builds on existing self-management practice and we have observed its efficacy in adolescents over a 36-h period at a clinical research facility [13]; however, episodes of hypoglycaemia that occurred after meals were most likely related to overestimation of prandial insulin doses and occurred even though basal insulin delivery was stopped by the control algorithm in the postprandial period.

The present study used the same protocol that we used previously in adolescents with suboptimum glycaemic control

Table 2. Glucose turnover from 08:00 hours on day 2 until midnight on day 2.

	Closed-loop with standard prandial boluses (n = 8)	Closed-loop with reduced prandial boluses (n = 8)	p
Insulin concentration, pmol/l*	317 (252, 435)	224 (204, 346)	0.009
Ra _{total} , μmol/kg/min	25.4 (21.0, 29.2)	26.3 (21.9, 28.0)	0.19
Rd, μmol/kg/min	25.2 (21.2, 28.8)	25.8 (21.0, 26.9)	0.46
Insulin metabolic clearance of insulin, ml/kg*	15.7 (8.3, 17.5)	16.6 (9.2, 20.9)	0.16
Insulin sensitivity, nmol/kg/min/pmol/l*	58.1 (36.3, 74.0)	81.2 (52.2, 94.0)	0.22

Values are median (interquartile range). Ra_{total}, total glucose appearance; Rd, glucose disposal.

*One subject was excluded as a result of having a much greater insulin concentration on both visits.

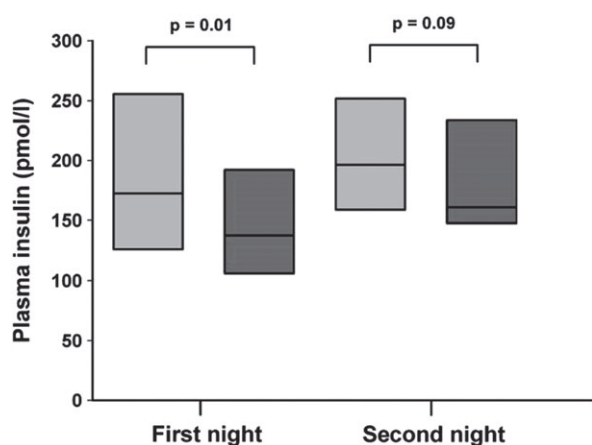


Figure 3. Mean plasma insulin levels on the first and second night during closed-loop therapy with standard prandial insulin boluses (light grey boxes) and closed-loop with reduced prandial boluses (dark grey boxes).

[13]. Only one episode of hypoglycaemia occurred 1.5 h after a meal when a standard bolus was given and none occurred when reduced boluses were administered, with no direct evidence that reduced bolusing may reduce the risk of hypoglycaemia. Closed-loop insulin infusion did not differ during the two study periods; the closed-loop algorithm did not increase basal insulin delivery when reduced boluses were given for meals to compensate for reduced meal insulin doses. As a consequence, both total insulin delivery and plasma insulin concentration were significantly lower when reduced boluses were administered; however, whereas reduced insulin levels during the day with reduced boluses were to be expected, the change in overnight insulin was unexpected. Reduced plasma insulin levels were documented overnight, as shown in Figures 2 and 3 and Table S2. Glucose turnover was unchanged between the two treatment approaches (Table 2) even during the overnight period (Table S2). The rate of R_d was comparable, but was associated with lower plasma insulin levels with reduced boluses suggesting saturation of insulin action as higher insulin levels did not lead to an increase in R_d . Alternatively, excess prandial insulin might increase counter-regulatory responses. A reduction in insulin exposure may be particularly beneficial during adolescence, at an age when increased insulin resistance and consequently higher insulin needs may lead to weight gain [25]. For this reason, closed-loop therapy with reduced meal boluses may be a more favourable alternative for adolescents.

The strength of the present study is its use of tracer dilution methodology to assess the metabolic consequences of reduced prandial boluses, the relatively long duration of the study, and the use of a well-studied controller. The weaknesses include the relatively small number of subjects but we targeted those most likely to benefit from closed-loop therapy with suboptimally controlled glucose levels.

In conclusion, closed-loop insulin delivery with 25% reduction of prandial boluses achieved similar glucose control and glucose turnover and may be preferable in adolescents with inadequate glucose control. Further investigations are warranted to investigate the reasons for the similar glucose control at lower insulin levels.

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Conflict of Interest

R. H. reports having received speaker honoraria from Minimed Medtronic, Lifescan, Eli Lilly, B. Braun and Novo Nordisk, serving on advisory panel for Animas, Minimed Medtronic and Eli Lilly, receiving licence fees from B. Braun, Beckton Dickinson and Medtronic, and having served as a consultant to Beckton Dickinson, B. Braun, Sanofi and Profil. M. E. W. has received licence fees from Beckton Dickinson and has served as a consultant to Beckton Dickinson. C. K. has served as a consultant to Medtronic International Trading Sàrl and Diabetes Technology Management. D. E., M. B., J. M. A., K. K., L. L., K. C., M. N., A. H., N. J., A. M. U., K. C. and P. C. declare no competing financial interests exist. R. H., D. B. D. and M. E. W. report patent applications.

D. E. and R. H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. H. coordinated the study. R. H., D. B. D., D. E., J. M. A. and M. E. W. co-designed the studies. D. E., M. B. and J. M. A. were responsible for screening and enrolment of participants and arranged informed consent from the participants. D. E., M. B., J. M. A., K. K., L. L. and K. C. provided patient care, collected the clinical and laboratory data, and contributed to biochemical analysis. M. E. W. carried out randomization. N. C. J. and A. M. U. carried out GCMS analysis. R. H., D. E., A. H., M. N., P. C. and C. K. carried out or supported the data analysis, including the statistical analyses. R. H. designed and implemented the glucose controller. R. H., D. B. D. and D. E. contributed to the interpretation of the results and the writing and critical review of the report.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart of study participants.

Table S1. Variable administration of glucose tracer [$6,6\text{-}^2\text{H}_2$]glucose during the study.

Table S2. Glucose turnover data overnight.

Table S3. Study outcomes based on sensor glucose levels.

Table S4. Study outcomes during the day-time and night-time based on plasma glucose.

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