The effect of closed-loop glucose control on C-peptide secretion in youth with newly diagnosed type 1 diabetes: the CLOuD RCT

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Scientific summary

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Background

Type 1 diabetes is characterised by autoimmune destruction of pancreatic beta-cells. At clinical diagnosis most people have residual pancreatic beta-cells which can continue to secrete insulin for several additional years. The Diabetes Control and Complications Trial (DCCT) showed that in adults, persistence of residual functioning beta-cells, measured by C-peptide secretion, is associated with improved glycaemic control, reduced risk of hypoglycaemia and lower incidence of microvascular complications. Interventions which can preserve endogenous insulin secretion prior to and following clinical diagnosis of type 1 diabetes are clinically important.

Previous studies have investigated whether an early period of intensive glycaemic control following diagnosis of type 1 diabetes can prevent the decline in endogenous insulin secretion, with conflicting results. An early exploratory study in adolescents reported improved C-peptide secretion at 12 months following a period of intensive insulin treatment in hospital for 2 weeks after diagnosis. A more recent study applying a short period of hybrid closed-loop within 7 days of diagnosis, followed by sensor-augmented pump therapy, did not alter C-peptide secretion at 12 months compared with standard care, but there was no difference in glucose control between the two treatment groups over the 12-month study period.

It has yet to be determined whether sustained intensive glycaemic control following diagnosis can ameliorate the decline in endogenous insulin secretion in youth with type 1 diabetes. Hybrid closed-loop systems have been shown to improve glucose control in youth and can accommodate variability in exogenous insulin requirements. We hypothesised that a sustained period of intensive glucose control with hybrid closed-loop following diagnosis of type 1 diabetes in children and adolescents can preserve C-peptide secretion compared to standard insulin therapy.

Objectives

The primary objective was to assess residual C-peptide secretion 12 months after diagnosis of type 1 diabetes in participants receiving either closed-loop insulin delivery or standard insulin therapy. The Closed Loop from Onset in Type 1 Diabetes (CLOuD) consortium secured external funding for participants to continue on beyond 12 months, but the funding by the National Institute for Health and Care Research (NIHR) and the results reported here refer only to the 12 months follow-up.

Secondary objectives included:

- biochemical assessment of how closed-loop insulin delivery affects glucose control in terms of safety and efficacy
- human factors assessments of emotional and behavioural characteristics of participants and family members and their response to closed-loop insulin delivery.

Methods

In this open-label, multicentre, randomised, single-period, parallel design trial, youth aged 10–16.9 years were recruited within 21 days of type 1 diabetes diagnosis from seven paediatric diabetes clinics in the UK (Cambridge, Edinburgh, Leeds, Liverpool, Nottingham, Oxford, Southampton). Participants and their families received structured diabetes education and training on the multiple daily injection regimen as

per standard clinical practice. Following recruitment, participants underwent a baseline mixed-meal tolerance test (MMTT) and were randomised to hybrid closed-loop or standard insulin therapy (control).

Participants randomised to the closed-loop group were trained to use the study insulin pump and glucose sensor prior to starting closed-loop insulin delivery within 6 weeks of diagnosis. Participants continued with closed-loop therapy at home with no remote monitoring or study-related restrictions. Participants randomised to standard insulin therapy received additional training to complement the core training and to match contact time with the closed-loop group. Participants could switch to insulin pump therapy and/or use flash/continuous glucose monitoring (CGM) or approved closed-loop systems if clinically indicated, applying National Institute for Health and Care Excellence (NICE) criteria. Participants were followed up at 3-monthly intervals. At each follow-up visit, glycated haemoglobin A1c (HbA1c) was measured and participants wore a masked glucose sensor for 14 days. MMTTs were conducted at 6, 12 and 24 months post diagnosis following an overnight fast.

The primary end point was the difference in mixed-meal C-peptide area under the curve (AUC) 12 months post diagnosis. Key secondary end points included time in target glucose range 3.9–10.0 mmol/l, glycated haemoglobin (HbA1c), and time in hypoglycaemia (< 3.9 mmol/l) at 12 months tested sequentially to control the type 1 error. Sensor glucose end points were based on data from a masked glucose sensor worn for 14 days. Analysis was by intention to treat. Additional secondary end points included fasting C-peptide measurements, HbA1c, sensor glucose data from intermittently applied masked sensor (time spent in target glucose range, time spent above and below target range, mean glucose and measures of glucose variability), daily insulin requirements, body mass index (BMI), blood pressure and lipid profile. Safety evaluation comprised the frequency of severe hypoglycaemia requiring assistance and diabetic ketoacidosis (DKA), and other adverse events (AEs) and serious adverse events (SAEs). Utility evaluation included assessment of the frequency and duration of use of the closed-loop (CL) system.

Human factors assessments included validated questionnaires for both participants and guardians evaluating the impact of the technology on quality of life and diabetes management. Qualitative assessment also comprised in-depth interviews with a subset of participants and parents after ≥ 12 months' experience using CL technology with data analysed thematically. Interviews were also conducted with health professionals delivering the CLOuD trial after they had ≥ 6 months' experience of supporting participants using a CL system and data were analysed thematically.

Results

We approached 162 eligible participants from 7 UK sites and randomised 97 participants [mean ± standard deviation (SD) age 12 ± 2 years, 44% female and 29% presenting with DKA at diagnosis], 51 to CL and 46 to control therapy. Mean time to randomisation from diagnosis was mean ± SD 9.5 ± 6.2 days. There were 10 post-randomisation withdrawals, 4 in the CL group and 6 in the control group. Two participants, one in each treatment group, were withdrawn by the clinic due to safety concerns and the other eight participant withdrawals were voluntary.

There was no difference in C-peptide AUC at 12 months (primary end point) between groups {geometric mean, interquartile range (IQR) closed-loop: 0.35 pmol/ml (0.16, 0.49) vs. control: 0.46 pmol/ml (0.22, 0.69); mean adjusted difference −0.06 [95% confidence interval (CI) −0.14 to 0.03 pmol/ml]; $p = 0.19$}. The proportion of time in target range 3.9 to 10.0 mmol/l based on 14-day masked LibrePro sensor glucose data at 12 months was 10 percentage points (95% CI 2 to 17 percentage points) higher in the CL group (mean ± SD 64 ± 14%) compared to control group (mean ± SD 54 ± 23%). As this end point did not reach the threshold of 0.01 in the analysis, other key secondary end points were not tested for statistical significance. Arithmetic mean HbA1c was lower in the CL group by 4 mmol/mol (0.4%)

[95% CI 0 to 8 mmol/mol (0.0% to 0.7%)] at 12 months. The mean difference in time spent < 3.9 mmol/l between groups was 0.9 percentage points (95% CI 1.0 to 2.8 percentage points) higher in the CL group at 12 months.

C-peptide AUC declined following diagnosis in both treatment groups. Plasma glucose AUC was similar between groups at 12 months and there was no difference in fasting C-peptide divided by fasting glucose between treatment groups. The proportion of participants with negative C-peptide stimulation in response to mixed-meal test was similar between treatment groups.

Mean glucose was 1.5 mmol/l (95% CI 0.5 mmol/l to 2.6 mmol/l) lower in the CL group than in control group at 12 months. Time in hyperglycaemia > 10.0 mmol/l was 11 percentage points (95% CI 3 to 19 percentage points) lower in the CL group compared to the control group at 12 months. Glucose variability measured by standard deviation (SD) was similar between CL and control groups, while coefficient of variation of glucose was 4 percentage points higher in the CL group at 12 months (95% CI 1 to 8 percentage points). The primary end point was similar in a per-protocol analysis using data from randomised participants in the CL group with at least 60% CL use and those in the control group who did not start insulin pump therapy.

Total daily insulin dose was similar between treatment groups, but there was a greater proportion of basal insulin (mean ± SD closed-loop 0.52 ± 0.31 U/kg/day, control 0.37 ± 0.26 U/kg/day) to bolus insulin (mean ± SD closed-loop 0.44 ± 0.22 U/kg/day, control 0.46 ± 0.23 U/kg/day) in the CL group at 12 months. Blood pressure, lipid profile and BMI percentile were similar between treatment groups.

In the CL group, median CL use was 66% (IQR 44–80) over the 12-month period. In the control group, 10% of participants (*n* = 4) were using insulin pump therapy and 57% (*n* = 21) were using a flash or real-time continuous glucose sensor at 12 months post diagnosis.

Three severe hypoglycaemic events occurred in the CL group (two participants), and one in the control group; one DKA occurred in the CL group and none in the control group. The number of other AEs (CL group 34, control group 37) and SAEs (CL group 2, control group 4) was similar between groups.

Responses to the Pediatric Quality of Life Inventory (PedsQL), hypoglycaemia fear survey (HFS), problem areas in diabetes (PAID) and Strengths and Difficulties Questionnaires (SDQs) were similar between treatment groups in both children and parents at 12 months. Scores for the INSPIRE (INsulin Dosing Systems: Perceptions, Ideas, Reflections and Expectations) questionnaire were high in children, teenagers and parents, suggesting positive expectancies regarding automated insulin delivery in this population.

In-depth interviews of 18 youths and 21 parents with ≥ 12 months' experience of using CL technology were undertaken. Interviews explored the impact of using CL systems on diabetes management practices and everyday family life. As reported by Lawton *et al.*

> *Participants reported very few disruptions to their lives when using a closed-loop system. Reports of family conflict were minimal as the closed-loop enabled dietary flexibility and glucose levels to be checked effortlessly. Adolescents described doing 'normal' activities without worrying about high or low glucose, and parents reported allowing them to do so unsupervised because the closed-loop would regulate their glucose and keep them safe. Some adolescents expressed concerns about the visibility of components and, to avoid stigma, described curtailing activities such as swimming. Participants described how the closed-loop enabled adolescents to be in control of, or create distance from, their diabetes.*
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> *Lawton J, Kimbell B, Rankin D, Ashcroft NL, Varghese L, Allen JM, et al.; CLOuD Consortium. Health professionals' views about who would benefit from using a closed-loop system: a qualitative study. Diabet Med: J Br Diabet Assoc 2020;**37**(6):1030–7.*

Interviews of multidisciplinary healthcare professionals (*n* = 22) providing support to trial participants explored the benefits, issues and challenges arising from introducing and using CL systems to support diabetes self-management. Lawton *et al*. reported that

> *interviewees described how, compared with other insulin regimens, teaching and supporting individuals to use a closed-loop system could be initially more time-consuming. However, they also noted that after an initial adjustment period, users had less need for initiating contact with the clinical team compared with people using pumps or multiple daily injections. Interviewees highlighted how a lessened need for ad hoc clinical input could result in new challenges; specifically, they had fewer opportunities to reinforce users' diabetes knowledge and skills and detect potential psychosocial problems.*
>
> *Lawton et al. (2020)*

We explored health professionals' views about who would benefit from using a CL system. Interviewees described holding strong assumptions about the types of people who would use the technology effectively prior to the trial. Interviewees described changing their views as a result of observing individuals engaging with the CL system in ways they had not anticipated. This included educated, technologically competent individuals who over-interacted with the system in ways which could compromise glycaemic control. Other individuals, who health professionals assumed would struggle to understand and use the technology, were reported to have benefited from it because they stood back and allowed the system to operate without interference. Interviewees concluded that individual, family and psychological attributes cannot be used as pre-selection criteria and ideally all individuals should be given the chance to try the technology.

Conclusions

The CLOuD study demonstrates that CL glucose control over a period of 12 months does not slow the decline in C-peptide secretion in children and adolescents with new-onset type 1 diabetes. Mean time in range was 10 percentage points higher and mean HbA1c was 0.4% (4 mmol/mol) lower in the CL group compared with the control group at 12 months, but these end points did not reach the pre-specified significance thresholds and it is possible that a greater improvement in glucose control with attainment of normoglycaemia could prevent the decline in C-peptide secretion. Further work may be needed to definitively rule out a role of glycaemic burden in the decline of C-peptide secretion. Total daily exogenous insulin requirements, a surrogate marker of residual insulin secretion, were similar between groups at all time points after diagnosis. This comparison may be hampered by any between-group differences in glycaemic control. It is likely that factors other than glycaemic control, such as autoimmune response, determine the rate of C-peptide decline following diagnosis of type 1 diabetes. It is possible that other factors act in concert with dysglycaemia on C-peptide secretion.

The present study demonstrates that hybrid CL is effective in new-onset type 1 diabetes in youth and can safely accommodate the variability in exogenous insulin requirements which occur with beta-cell recovery post diagnosis. Glycaemic control was sustained over 12 months in the CL group, whereas glycaemic control started to deteriorate in the control group at 6 to 9 months after diagnosis. At 12 months post diagnosis, only 56% of youth in the control group (78% in the CL group) were able to achieve a HbA1c of < 58 mmol/mol (< 7.5%) which is above the current national and international glycaemic targets. This highlights the need for improved therapies to allow youth to achieve recommended glycaemic targets from onset of type 1 diabetes irrespective of the lack of effect on residual C-peptide secretion.

Strengths of this study include the multicentre, randomised parallel design and the 1-year study duration. We applied no exclusions at enrolment such as technology propensity or healthcare professional considerations about suitability, minimising selection bias. The study population are representative of the general population of youth newly diagnosed with type 1 diabetes. There were no

limitations to diabetes therapies used in the control group, supporting generalisability of the findings. This study had limitations. There was no central measurement of auto-antibodies at diagnosis. There was imbalance in the rate of DKA at diagnosis which is associated with a more rapid decline in C-peptide secretion. The rate was higher in the CL group (33%) than in the control group (24%) but this was adjusted for in the analyses.

In conclusion, a sustained period of hybrid CL glucose control following diagnosis of type 1 diabetes in children and adolescents does not appear to prevent the decline in residual C-peptide secretion.

Trial registration

This trial is registered as Clinicaltrials.gov NCT02871089.

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