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Study protocol: a randomised controlled proof-of-concept real-world study – does maximising time in range using hybrid closed loop insulin delivery and a low carbohydrate diet restore the glucagon response to hypoglycaemia in adults with type 1 diabetes?

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ABSTRACT

Introduction People with type 1 diabetes (T1D) develop an impaired glucagon response to hypoglycaemia within 5 years of diagnosis, increasing their risk of severe hypoglycaemia. It is not known whether eliminating hypoglycaemia and hyperglycaemia allows recovery of this glucagon response. Hybrid closed loop (HCL) technologies improve glycaemic time in range (TIR). However, postprandial glycaemic excursions are still evident. Consuming a low carbohydrate diet (LCD) may minimise these excursions.

Methods and analysis This feasibility study will assess if maximising TIR (glucose ≥3.9 mmol/L≤10 mmol/L) using HCL systems plus an LCD (defined here as <130 g carbohydrate/day) for >8 months, restores the glucagon response to insulin-induced hypoglycaemia. Adults (n=24) with T1D (C-peptide <200 pmol/L), naïve to continuous glucose monitoring (CGM) and HCL systems, will be recruited and randomised to: group 1 (non-HCL) to continue their standard diabetes care with intermittent blinded CGM; or group 2 (HCL-LCD) to use the HCL system and follow a LCD. Baseline data on diet and glycaemia will be collected from all participants. The HCL-LCD group will then enter a 2-week run-in to acclimatise to their devices. Throughout, the HCL-LCD group will have their glucose closely monitored and adjusted aiming for glycaemic TIR >70%. Participants will have their glucagon response to hypoglycaemia measured at the beginning and 8 months later at the study end using a stepped hyperinsulinaemic hypoglycaemic clamp, in combination with the stable isotopes 6,6-$^{2}H_{2}$-glucose (D2-glucose) and 1,1,2,3,3-$^{2}H_{5}$-glycerol (D5-glycerol) to assess glucose and glycerol kinetics. The impact of hypoglycaemia on symptoms and cognitive function will be assessed during each clamp study. The primary outcome is the difference in the glucagon response to hypoglycaemia between and within groups at baseline versus study end.

Ethics and dissemination Ethical (20/SS/0117)/institutional review board (2021/0001) approval has been obtained. The study will be disseminated by peer-reviewed publications and conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Uses technology that is CE marked/FDA and MHRA approved and may enable these technologies to become more widely available to people with type 1 diabetes (T1D) through healthcare systems.
⇒ Will aid our understanding of the pathophysiological mechanisms in T1D including whether the glucagon response to hypoglycaemia once impaired can be restored.
⇒ Study participants will need to be able to use the technology, therefore favouring such people who may self-select to do the study.
⇒ This is a small study and larger numbers may be required to assess if increasing glycaemic time in range restores glucagon secretion to insulin-induced hypoglycaemia.

Trial registration number NCT04614168.

INTRODUCTION

In type 1 diabetes (T1D) there is a destruction of pancreatic beta cells by autoimmune processes with resultant low or absent circulating C-peptide concentrations. People with the condition are dependent on exogenous insulin to control their blood glucose levels.[1] However, a common side effect of exogenous insulin therapy is hypoglycaemia.[2]

Glucagon, the pancreatic islet alpha cell product, is a sensitive regulator of glucose homeostasis. In vivo in humans it plays a critical role in the counterregulatory response to hypoglycaemia.[2–6] Almost all people with T1D develop a specific defect in alpha cell glucagon secretion within 5 years of diagnosis[7] with an inadequate response to

hypoglycaemia, increasing their risk of severe hypoglycaemia.[8] Residual C-peptide secretion (in the so called micro-secretors) may influence this response[9] with greater time in range (TIR)[5] and diminished glycaemic variability and hypoglycaemia[10] versus those with undetectable C-peptide concentrations. The fact that glucagon concentrations may also be inappropriately high postprandially[11] and that there is evidence for intact secretion in other scenarios,[12] shows that alpha cell function is not lost but is dysregulated. The aetiology of this defect is not fully understood. A mouse model of neonatal diabetes showed chronic hyperglycaemia leads to changes in islet cell morphology and function without a change in islet cell number or density.[13] Structural and electrophysical changes in beta cell function were shown and attributed to chronic hyperglycaemia. The same group subsequently showed significant glycogen accumulation which they postulated contributed to the insulin secretory defect of the beta cells.[14] In both studies reduced glucose levels led to restoration of normal glucose homeostasis and a reversal of the morphological changes of the beta cell. Although no dynamic assessment of alpha cell function was made, the near normalisation of glucose homeostasis suggests restoration of both alpha and beta cell function.

Continuous glucose monitoring (CGM) has made it possible to quantify glycaemic TIR. In range blood glucose is defined as ≥3.9 and ≤10.0 mmol/L.[15] The current recommended TIR goal is >70%, which equates to an HbA1c of ~53 mmol/L, with <4% time with blood glucose <3.9 mmol/L.[16] The short-term and long-term benefits of achieving glycaemic TIR in T1D are clear.[17 18] These glycaemic TIR goals have been largely defined from trials using sensor augmented and hybrid closed loop (HCL) systems and are more challenging to achieve in those not using these devices.[19 20] People using HCL do see significant improvements in glycaemic TIR, particularly overnight.[21–25] However, postprandial glycaemic excursions remain and contribute significantly to overall glycaemic burden.[26] There is evidence that restricting the amount of carbohydrates eaten can be a safe and effective way to improve glycaemic control in T1D. There are varying definitions of what constitutes a low carbohydrate diet (LCD) in T1D. Two recent reviews suggested LCD may be defined as <130 g carbohydrate per day or <26% of total daily energy intake as carbohydrate.[27 28] Studies incorporating LCDs in people with T1D show improved HbA1c values,[29 30] reduced glycaemic variability and greater glycaemic TIR in participants administered a low versus a high carbohydrate diet.[31] However, many of these studies recruited small groups of motivated participants and lacked control groups. The gold standard method for measuring hormone responses to hypoglycaemia in T1D is the hyperinsulinaemic hypoglycaemic clamp (clamp).[32–34] During a clamp, glucose and glycerol turnover can be assessed by infusing the stable non-radioactive isotopes D2-glucose and D5-glycerol, respectively; these tracers are safe in humans.[34–39]

HYPOTHESIS

Increasing glycaemic TIR using HCL systems in combination with an LCD for a period of >8 months will increase the glucagon response to insulin-induced hypoglycaemia in people who have long standing T1D.

METHODS AND ANALYSIS

Overview

This is a proof-of-concept study involving 24 participants aged ≥21 years who have had T1D for ≥5 years (figure 1). It will assess if a glycaemic TIR >70% for ~8 months, using HCL systems and an LCD, leads to a significant restoration of the glucagon response to insulin-induced hypoglycaemia. It has not previously been investigated if increasing TIR so as to reduce exposure to hyperglycaemia restores this hormonal response. This is therefore a feasibility study that can be used to inform power calculations for future randomised controlled trials. The study commenced participant recruitment in August 2021 and aims to end recruitment in December 2022. The last participant is expected to exit the study in July 2023.

Participants will be randomised to one of two study groups.

Group 1 is the non-HCL group who will remain on their prestudy diabetes management and not be on closed-loop systems. They will undergo 2 weeks of blinded CGM monitoring on three occasions: immediately postrandomisation, at study mid-point and at study end to assess their glycaemic variability and TIR. During each of these periods they will also complete a 7-day food diary. No adjustments to their diet will be advised.

Group 2 is the HCL-LCD group. Postrandomisation but preceding administration of the devices and dietary advice they will also undergo 2 weeks of blinded CGM monitoring, following which they will be placed on the study devices and advised with respect to a LCD. They will use CGM for the rest of the study .

All participants will undergo a clamp, with simultaneous stable-isotope studies with D2-glucose and D5-glycerol, at the beginning of the study and 8 months later to assess their hormonal and symptomatic response to hypoglycaemia as well as glucose and glycerol kinetics. They will complete questionnaires relating to hypoglycaemia awareness, quality of life (QoL) and treatment satisfaction on study entry and completion (box 1).

The Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used to inform this protocol.[40]

Study devices and LCD

Devices

All devices used in the study are U.S. Food and Drug Administration (FDA), Medicines & Healthcare products Regulatory Agency (MHRA) approved and Conformitè Europëenne (CE) marked.

The Tandem t:slim X2 is an insulin pump with integrated Control-IQ algorithm technology[41] (figure 2). This

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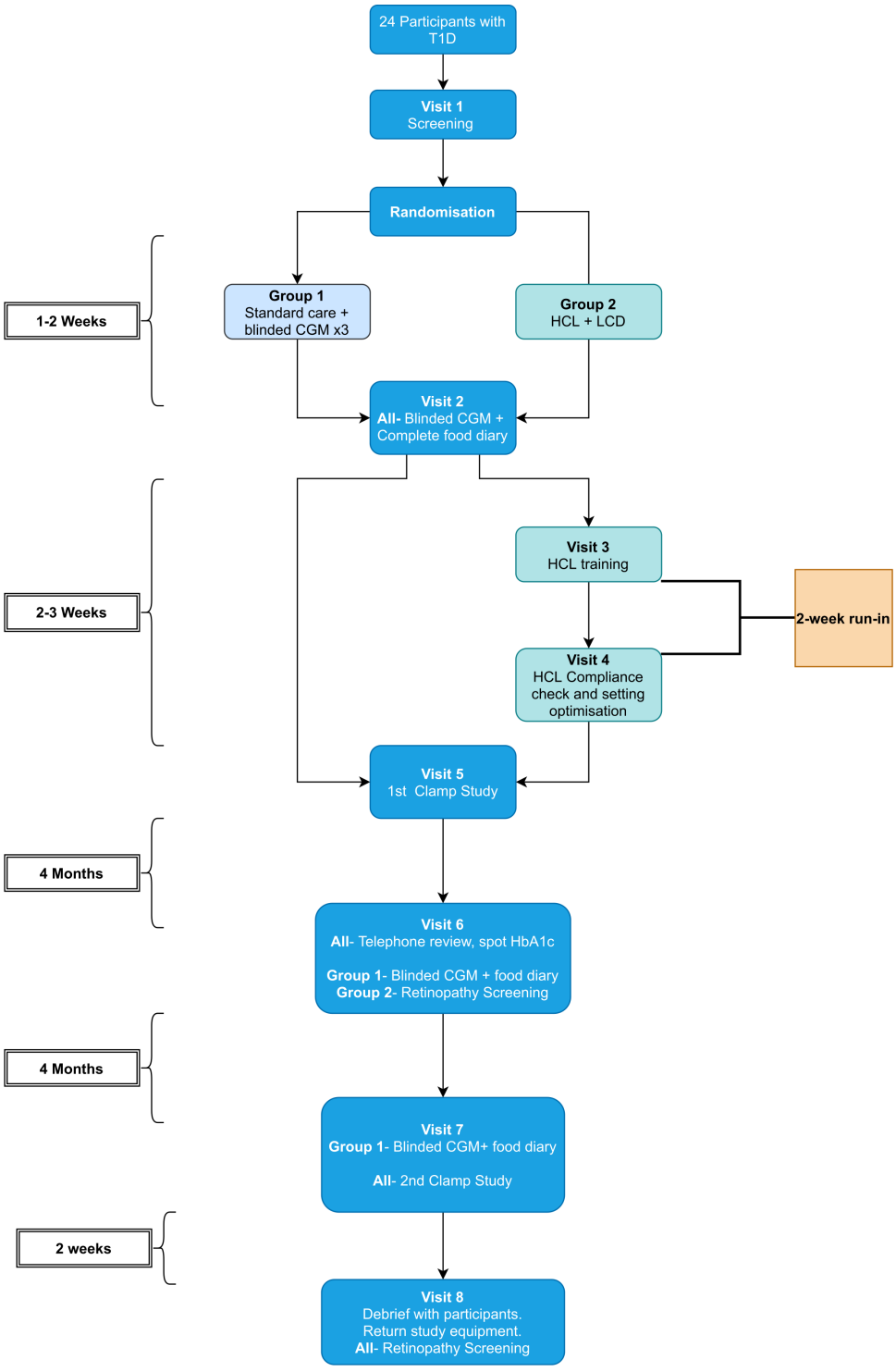

Figure 1 Study schedule. CGM, continuous glucose monitoring; HCL, hybrid closed loop; LCD, low carbohydrate diet; T1D, type 1 diabetes.

algorithm uses glucose data, received every 5 min from the CGM device, to (i) vary basal insulin delivery, (ii) give automatic correction boluses and (iii) suspend insulin delivery if required. Adjustments made by the algorithm are based on the 30 min predicted blood glucose level. The infusion set is inserted every 3 days using an automated application device. The system has been shown to improve TIR without increased risk of hypoglycaemia in both adults[42] and children.[25]

The Dexcom G6 CGM[43] (figure 3) will be used. A sensor is inserted under the skin which measures interstitial fluid glucose which is transmitted via Bluetooth to the display device (a smart device and/or Dexcom receiver) every 5 min. The sensor is changed every

Box 1 Questionnaires

Psychological and device related questionnaires
⇒ EQ-5D-5L.[54]
⇒ Hypoglycaemia Fear Survey.[55]
⇒ Hypoglycaemia Confidence Scale.[46]
⇒ Diabetes Technology Attitudes (DSAT).[56]
⇒ Diabetes Technology Questionnaire.[57]

Hypoglycaemia awareness questionnaires
⇒ Gold Score.[58]
⇒ Clarke Score.[59]

10 days and no calibration against blood glucose is required.

Data from the participants' devices will be available for study staff to review remotely using the secure web-based systems Dexcom Clarity[44] and Tandem t:connect.[45] Data are automatically uploaded to Dexcom Clarity from the CGM device but participants will be required to upload their insulin pump data at least once a week during the study by connecting their pump to a computer via a USB.

If the data show that the participant is spending time out of the glycaemic target range they will be contacted by study staff to discuss appropriate adjustments to insulin pump settings or diet.

Diet

All participants routinely receive education in carbohydrate counting and insulin dose adjustment, for example, Dose Adjustment for Normal Eating[46] before recruitment to the study. The HCL group will receive additional advice from healthcare professionals in this study regarding meal plans for a LCD. They will aim to consume 30–40 g of carbohydrate per main meal portion and 10–15 g of carbohydrate per snack with <130 g/day of carbohydrate.[27 28] They will be provided with meal plans, food scales (Salter 1035 Kitchen scales) and the Carbs and Cals mobile phone application or book to aid carbohydrate counting.[47] We routinely advise with respect to this diet for patients following islet transplantation.[48]

Participants

The study will recruit 24 adults (age ≥21 years) who have had T1D for ≥5 years from the National Health Service (NHS) Lothian pump waiting list and the T1D clinic.

Figure 2 Tandem t:slim X2 insulin pump and infusion set (right). Dexcom G6 Sensor (left). All images reproduced with permission.

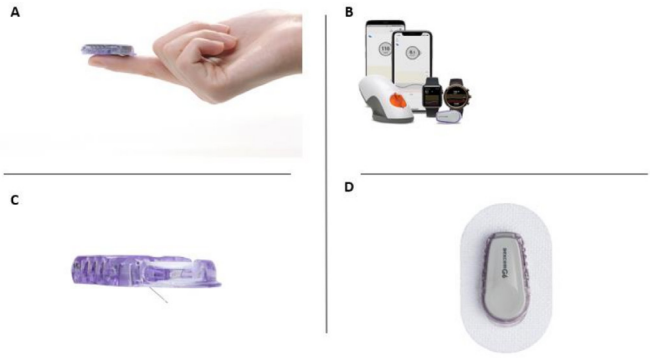

Figure 3 Dexcom G6 continuous glucose monitor and devices. (A) G6 transmitter and sensor; (B) Dexcom G6 CGM system; sensor applicator, transmitter and display devices; (C) G6 sensor with sensor cannula visible; (D) G6 sensor with transmitter and adhesive patch. All images reproduced with permission.

Eligibility criteria

The inclusion and exclusion criteria are summarised in table 1.

Recruitment

Participants will be recruited from three hospitals in the Lothians: Edinburgh Royal Infirmary (ERI), Western General Hospital, Edinburgh and St John's Hospital, Livingston.

Potential participants will be contacted via letter inviting them to contact study staff if they are interested in taking part in the study. If they contact study staff the protocol will be discussed over the phone and the participant information leaflet (PIL) and consent form sent to them to read.

Potential participants will be given >5≤14 days to decide whether to take part in the study after receiving the PIL. They will be given contact details for study staff should they wish to ask further questions during this time. A follow-up phone call will be made to participants if they do not make contact after 14 days.

Consent and enrolment

Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained from potential participants.

Study schedule

Face-to-face visits will take place at the ERI Clinical Research Facility (CRF) and the ERI. Other visits will take place by telephone. The study schedule is shown (figure 1). In the monitoring period between visit 5 and 6 and visit 6 and 7 advice will be given to participants if they are not reaching glycaemic TIR >70%.

Study visit 1: screening and randomisation

Participants who decide to enrol in the study will attend the CRF. They will meet with study staff and complete a written consent form.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
T1D with C-peptide <200 pmol/L	Current use of non-approved closed loop system or predictive low glucose suspend insulin pump
Age 21–65 years	Regular use of real-time CGM in the preceding 3 months
T1D for ≥5 years	History of DKA in the preceding 6 months
HbA1c ≥53 mmol/mol	Inability to safely use the technology in this study
Normal renal function	History of: ► Haemophilia. ► Cystic fibrosis. ► Pancreatic disease or complete pancreatectomy. ► Ischaemic heart disease. ► Epilepsy. ► Hypoglycaemia induced seizures. ► Severe reaction or allergy to adhesive necessary for the study
Normal thyroid function	Unable to adhere to study timetable
Willingness to monitor blood ketones daily	Unable to give informed consent
Use of freestyle libre device permitted in group 1	Concurrent use of non-insulin glucose lowering agents (GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulphonylureas)
	Concurrent use of SSRIs or other medication that effects blood glucose
	A condition, which in the opinion of the investigator, would put the patient or study at risk
	Pregnant or planning a pregnancy
	Proliferative retinopathy
	HbA1c ≥75 mmol/mol

CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; SSRI, selective serotonin reuptake inhibitor; T1D, type 1 diabetes.

After informed consent has been obtained the participant will be evaluated for study eligibility. They will have their medical history documented and a physical examination. Local laboratory testing will be arranged to screen for exclusionary medical conditions. Participants who have not had retinopathy screening in the previous 6 months will have this arranged. They will complete questionnaires to assess hypoglycaemia awareness (the Clarke and Gold score), and validated psychological and device related questionnaires (box 1).

Those deemed ineligible will be contacted, the reasons explained and appropriate follow-up arranged.

Randomisation

Participants will be randomised at the end of visit 1. Participants will choose a sealed envelope with the assigned group enclosed, at random.

Those randomised to the HCL-LCD group will be sent training materials for the Tandem t: slim X2 insulin pump and Dexcom G6 CGM.

Study visit 2: baseline data collection

All participants will attend the CRF and be fitted with a Dexcom G6 CGM. They will use this, blinded, for 20 days to gain experience in its insertion and for the research team to obtain baseline glycaemic data. They will be required to insert two CGM devices to cover this 20-day period with support from study staff as required. As participants will not be able to view their CGM data during this time they will continue to monitor their own glycaemic control.

Participants will be asked to complete a 7-day food diary during this period of CGM monitoring.

Study visit 3: HCL-LCD training

Participants randomised to the HCL-LCD group will attend the CRF to be fitted with a Tandem t:slim X2 insulin pump, with the Control IQ algorithm, and Dexcom G6 device. This will take place after the 20-day period of blinded CGM monitoring. Participants will be trained in the use of the pump that is in-line with what is received by NHS patients commencing on insulin pump therapy. They will review online training materials and read the user guide for the device before attending this visit. At this training session their knowledge of the pump will be checked against a standard checklist. From this time in the study the HCL-LCD group will be able to view their CGM data and use this to make treatment decisions.

They will also receive advice from the study team with respect to the LCD and management of insulin doses for their carbohydrate intake. This advice will be informed by the completed food diary.

Participants will be given blood ketone testing sticks and asked to check ketones daily. If blood ketones are

>1.5 mmol/L they will be asked to contact the study team or the out of hours care team.

Study visit 4: run-in period for HCL-LCD group

The HCL-LCD group will enter a 2-week study run-in period to adjust to their new equipment.

Data from their devices will be monitored remotely using Dexcom Clarity and Tandem t:connect by study staff who will be contactable if there are any issues. At the end of this run-in period participants will meet with study staff on the telephone, or in person if they prefer, to assess:

1. Compliance with the use of the study devices.
2. Any skin reactions in areas where a CGM sensor or pump set site was worn.
3. Proficiency with the CGM and insulin pump technology.
4. Eligibility to continue in the study.
5. CGM readings being obtained on >11 of the previous 14 days.
6. Control IQ use >90% over 14 days.

Additional visits and phone contacts for further training are at the investigator's discretion.

The pump settings (insulin: carbohydrate ratios, basal rates and insulin sensitivity) will be reviewed and optimised as appropriate based on the participant's CGM data over the run-in period.

Study visit 5: hypoglycaemic clamp and stable isotope infusion study

All participants will attend the CRF, the HCL-LCD group after the 2-week run-in period, for the first clamp study (figure 4). The clamp study will last for 5–6 hours.

In the 48 hours preceding the study participants will be asked to avoid moderate/high intensity exercise and any medication that may affect blood glucose, for example, salicylates and quinolone antibiotics.

In the 24 hours preceding the study participants will be asked to do the following:

- Avoid alcohol and caffeine.
- Consume a moderate carbohydrate (40–60 g) evening meal.
- Fast for >8 <10 hours before presenting to the CRF at 07:30.
- Avoid hypoglycaemia—the study will be postponed if the blood glucose is <3 mmol/L for >20 min

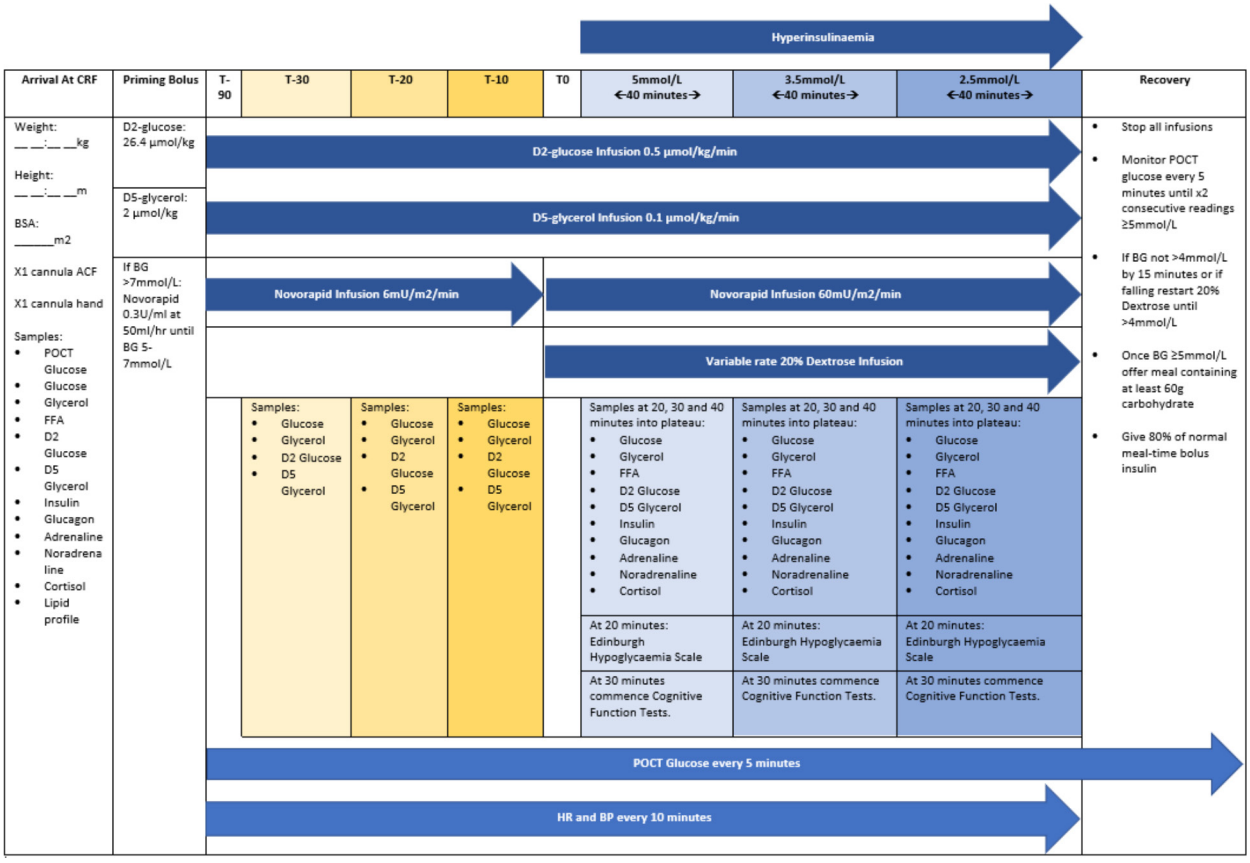

Figure 4 Hyperinsulinaemic hypoglycaemic clamp study with stable isotopes. Stable isotope infusions commence, after a priming bolus, concurrently with a basal insulin infusion 90 min before the hyperinsulinaemic clamp study (T-90). Samples for isotope enrichment and steady state are taken 30 (T-30), 20 (T-20) and 10 (T-10) min before the clamp. At time 0 (T0) the hyperinsulinaemic clamp study begins. During the clamp each glucose plateau is held for 40 min with time between each plateau for the glucose to fall to the next plateau. ACF, antecubital fossa; BG, blood glucose; CRF, clinical research facility; FFA, free fatty acids; POCT, point of care glucose.

as antecedent hypoglycaemia is known to affect the counterregulatory response to subsequent hypoglycaemia.[49]

- If on basal/bolus insulin regimen: reduce basal insulin the night before by 20%.
- If on the HCL system: place the insulin pump on exercise settings the morning of the clamp.

When participants arrive at the CRF they will have anthropometric measurements taken to calculate their body surface area (BSA) and their insulin infusion rates accurately. BSA will be calculated using the Mosteller formula:

$$\text{BSA } (m^2)=\sqrt{((\text{height (cm)}\times\text{weight (kg)})/3600}$$[50]

They will also have a pregnancy test if applicable.

Two peripheral intravenous cannulae will be inserted. The first of these will be inserted retrogradely in the non-dominant hand which will be placed in a heated box at 55°C to arterialise venous blood for blood sampling during the study.[51] The second cannula will be inserted into the antecubital fossa to administer the infusions. Baseline bloods will be obtained for: glucose, insulin, glucagon, glycerol, D2-glucose (background), D5-glycerol (background), cortisol, epinephrine, norepinephrine, free fatty acids and lipid profile at the time of insertion.

Hyperinsulinaemic hypoglycaemic clamp and stable isotope study

A priming dose of Novorapid (0.3 U/mL at 50 mL/hour) will be given if blood glucose is >7 mmol/L until it is ≥5<7 mmol/L. This will be followed by a basal insulin infusion (Novorapid 6 mU/m^2/min) to maintain euglycaemia in the first 90 min of the isotope infusions. Blood glucose will be monitored every 5 min using a point of care glucose analyser (Biosen C line GP+glucose analyser).

A primed continuous infusion of D2-glucose (priming 24.6 µmol/kg, infusion 0.5 µmol/kg/min) and D5-glycerol (priming 2 µmol/kg, infusion 0.1 µmol/kg/min) (Euriso-Top Isotope Laboratories) will be commenced 90 min before (T-90) the hyperinsulinaemic clamp study and maintained for the duration of the study. Blood samples will be taken for glycerol, glucose, D5-glycerol and D2-glucose at 30 (T-30), 20 (T-20) and 10 min before (T-10) the hyperinsulinaemic clamp to measure steady-state glucose and glycerol concentrations and isotopic enrichment.

Throughout the clamp blood glucose will be analysed every 5 min. Participant's heart rate will be monitored continuously throughout the hypoglycaemia clamp and blood pressure will be monitored every 10 min.

At the start of the hyperinusulinaemic clamp (T0) the insulin infusion rate will be increased to 60 mU/m^2/min and a variable rate 20% dextrose infusion will also be commenced. The rate of the dextrose infusion will be adjusted as required to obtain the desired glucose nadir.

Box 2 Tasks during clamp study plateaus

Assessment of symptoms

⇒ Edinburgh Hypoglycaemia Scale.[60]

Cognitive function tests

⇒ Trail Making Test.[61 62]
⇒ Digit Span Test.[63]
⇒ Digital Symbol Substitution Test.[64]
⇒ Four Choice Reaction Time Test.[65]

During each plateau participants will complete the Edinburgh Hypoglycaemia Scale to assess their symptoms and cognitive function tests.

The participant's blood glucose will be adjusted in three steps to: 5 mmol/L, 3.0 mmol/L and 2.5 mmol/L. Each plateau will be maintained for 40 min. Blood will be drawn on three occasions during each plateau to measure: glucagon, insulin, glucose, glycerol, free fatty acids, D2-glucose, D5-glycerol, epinephrine, norepinephrine and cortisol at steady state. At the mid-point of each glucose plateau participants will rate their symptoms of hypoglycaemia using the Edinburgh Hypoglycaemia Scale and complete cognitive function tests (box 2).

At the end of the final glucose plateau all infusions will be stopped. Blood glucose will continue to be monitored every 5 min until two consecutive readings ≥5 mmol/L. If the blood glucose is not ≥4 mmol/L, 15 min after the infusions have stopped the 20% dextrose infusion will be restarted until blood glucose is ≥4 mmol/L. Once the blood glucose is ≥5 mmol/L the participant will be offered a meal containing at least 60 g of carbohydrate. They will be given 80% of their normal meal-time bolus insulin to cover the carbohydrates in the meal. Participants will be able to leave the CRF once they have finished their meal and their blood glucose is stable.

Samples taken during the clamp will be centrifuged and stored at −80°C before analysis. Each participant will have their samples from both clamp studies analysed on the same day to ensure laboratory conditions do not bias the results. Samples will be analysed as per manufacturer instructions. The hormone assays used are detailed in table 2.

Monitoring period

Group 1 (non-HCL group)

Participants will continue their standard diabetes care and will have two further 20-day periods of blinded CGM monitoring during the study with the aim of collecting ≥14 days of data. They will be asked to complete a 7-day food diary during this period and continue monitoring their own glucose readings.

The periods of CGM monitoring will be: (i) at 4 months (study mid-point) and (ii) at 8 months postrandomisation preceding the second clamp study.

Group 2 (HCL-LCD group)

Participants will continue on the study devices with a glycaemic TIR aim of >70% in each 24-hour period. They

Table 2 Hormone assays

Hormone	Insulin	Glucagon	Epinephrine and norepinephrine	Cortisol
Assay	Mercodia insulin ELISA	Mercodia glucagon ELISA	LDN 2-CAT (A-N) Research ELISA	LDN cortisol ELISA
Measurement range	3–200 mU/L	1.5–130 pmol/L	Epinephrine: 1–200 ng/mL Norepinephrine: 5–1000 ng/mL	20–800 ng/mL
Sensitivity	<1 mU/L	0.75 pmol/L	Epinephrine: 6.6 pg/mL Norepinephrine: 2,6 pg/mL	1.3 ng/mL
Intra-assay CV	2.4%–4%	2.1%–14%	Epinephrine: 9.3-17.1% Norepinephrine: 8.4-15.6%	3.2%–8.1%
Inter-assay CV	2.6%–3.6%	7.0%–16%	Not reported	6.5%–7.7%

The hormone assays used along with their corresponding range, sensitivity and coefficient of variation.
CV, coefficient of variation;

will be asked to upload their insulin pump data at least once weekly to Tandem t:connect. Members of the study team will review this data and the data that automatically uploads to Dexcom Clarity.

Staff will contact participants when:

1. Glycaemic TIR <70% and adjustments are required to insulin pump settings.
2. The participant is not changing the insulin pump set every 3 days.
3. The participant requires reinforcement about the LCD or carbohydrate counting.
4. The participant is experiencing multiple alarms or error codes.

Participants will have contact details for study staff and will be able to contact them on an ad hoc basis throughout the study.

Study visit/consultation 6: assessment of metabolic control and retinopathy screening at study mid-point

A scheduled mid-point telephone consultation at 4 months will be arranged for all participants. This can be a face-to-face appointment if requested.

All participants will have an HbA1c measured at 4 months. This will be done using a home testing kit (Exeter Clinical Laboratory International). Samples are collected via a fingerstick blood test into a small EDTA tube and posted to the reference laboratory in Exeter for analysis.

Participants in the HCL-LCD group will undergo retinopathy screening 3–4 months after starting their insulin pump in-keeping with local NHS protocols.

Study visit 7: hyperinsulinaemic hypoglycaemic clamp study 2

All participants will undergo a second hypoglycaemic clamp study at 8 months (figure 4).

Participants will complete the questionnaires (box 1).

Study visit 8: feedback and retinopathy screening at study end

Within 2 weeks of visit 7, participants will meet face-to-face with study staff. They will return their study devices and completed questionnaires and be given the opportunity to discuss the study and provide feedback. Staff will review the blinded CGM data with the non-HCL group during this visit.

All participants will undergo repeat retinopathy screening at the end of the study.

Analysis

Primary endpoints

The primary analyses will evaluate between and within group differences in the glucagon response to hypoglycaemia at the first and second clamp studies.

Mean (SD) difference in glucagon response between clamp studies will be tabulated by treatment group. A regression model will be used to compare differences between the two groups. Area under the curve (AUC) and incremental AUC for glucagon response will also be calculated and compared within and between studies.

Subgroup analyses will be performed on the glycaemic TIR at study end points as well as incremental changes per se, to determine how absolute and incremental increases in TIR impact the primary study outcome. Further analyses will be performed as appropriate for example incorporating reductions in hyperglycaemia and hypoglycaemia and numbers permitting examining the primary outcome in those with impaired awareness of hypoglycaemia.

Secondary endpoints

The following outcomes will be compared within study participants and between the two groups at the beginning and end of the study:

- Time in glycaemic range (3.9–10 mmol/L).
- Time spent below target glycaemic range (<3.9 mmol/L) (TBR).
- Time spent above target glycaemic range (>10 mmol/L) (TAR).
- The change in counterregulatory hormone responses measures during normoglycaemia and hypoglycaemia compared between clamp study at baseline and study end:
  - Cortisol

  - Epinephrine
  - Norepinephrine
- Endogenous glucose production as measured in isotope studies using D2-glucose.
- Glycerol kinetics as measured in isotope studies using D5-glycerol.
- HbA1c.
- QoL as measured by the EQ5D-5L.
- Changes in emotional distress related to diabetes as measured by the Diabetes Distress Scale.
- Attitudes to diabetes technologies as measured by the Diabetes Technology Questionnaire and the Diabetes Technology Attitudes Survey.
- Change in fear of hypoglycaemia measured by the Hypoglycaemic Fear Survey.
- Change in confidence in managing hypoglycaemia as measured by the Hypoglycaemic Confidence Scale.
- Hypoglycaemic awareness as measured by the Edinburgh Hypoglycaemia Scale and the Clark and Gold Score.
- Cognitive function during hypoglycaemia (box 2).

Glucose thresholds for the onset of hormone responses, symptoms and cognitive dysfunction will be defined as previously described.[32 52 53] The glycaemic threshold for onset of hormone response will be defined as an increase in hormone concentration ≥2 SD above the mean in euglycaemia. The total AUC and incremental areas under the curve will be calculated for each hormone and compared between groups.

The isotopic enrichments of glucose and glycerol will be determined by mass spectrometry. Steele's non-steady state equation will be used to calculate the isotope kinetics, rate of appearance and rate of disappearance.[34 38]

Descriptive statistics will be expressed as mean (SD) for normally distributed data and medians with IQR otherwise. A p value of <0.05 will be deemed significant.

PATIENT AND PUBLIC INVOLVEMENT

Patients were involved in the development of the study concept via the Helmsley Charitable Foundation Trust which has patient representation. The Helmsley Charitable Foundation Trust has provided funding for this study.

ETHICS AND DISSEMINATION

Ethical opinion by the South East Scotland REC 01 (reference number 20/SS/0117).

The findings will be disseminated by peer-review publications and conference presentations and will be communicated in writing to the participants in the study.

Ethical considerations

All laboratory specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The chief investigator and study site staff will not disclose or use for any purpose other than performance of the study, any data, record or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

STUDY MANAGEMENT

Adverse events

Participants will be asked about the occurrence of adverse events (AE) and serious adverse events (SAE) at every visit. Open-ended and non-leading verbal questioning will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments, for example, laboratories.

All AEs/SAEs will be documented in the participant case file and reported to the sponsor.

Data management

All investigators and study site staff will comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will only contain non-identifiable data.

Dexcom clarity and Tandem t:connect are secure and encrypted platforms. No interface with medical records is required for them to operate and only authorised users can access the data. The Tandem t:connect application uses a stand-alone relational database that is setup specifically for each study.

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Contributors SF conceptualised the study. FB, NB and SF all designed the study protocol. FB NB and SF wrote the manuscript. All authors critically reviewed the report.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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