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Effect of breaking up sitting with regular active breaks on glucose management and vascular function in adults with type 1 diabetes who use hybrid closed-loop insulin delivery systems: a randomised crossover trial protocol

Joseph Graham Jenkins [1], Matthew Cocks,[2] Samuel J E Lucas [1], Catarina Rendeiro,[1] Tiago Peçanha,[3] Joseph Maxwell,[2] Jacob Harrison Tennant [1], Georgia Philpot,[1] Parth Narendran,[4,5] Robert Andrews,[6] Sam N Scott,[7] Katie Hesketh[1]

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ABSTRACT

Sedentary behaviour is associated with an increased risk of cardiovascular disease and all-cause mortality in people with type 1 diabetes (T1D). Recent research has found that interrupting prolonged sitting with low-intensity activity acutely improves glycaemic management in people with T1D who use multiple daily insulin injections or continuous subcutaneous insulin infusion. However, the acute glycaemic effects of breaking up sitting with low-intensity walking on people with T1D using hybrid closed-loop (HCL) insulin systems are yet to be examined. The primary aim of the present study is to investigate the influence of breaking up 7 hours of sitting with 3 min intervals of low-intensity walking every 30 min on glucose management in individuals with T1D who use HCL systems. Adults with T1D (n=24), who use HCL systems, will complete two experimental conditions in this randomised cross-over trial. One condition will require sitting uninterrupted for 7 hours (Sedentary), while the other will require breaking up 7 hours of sitting with 3 min of low-intensity walking every 30 min (Active Breaks). During both conditions, interstitial glucose concentrations (via CGM) and insulin administration (via HCL) will be recorded throughout. In addition, peripheral vascular function (via flow-mediated dilation) and cerebral vascular function (via CO_2 reactivity) will be measured at baseline and post. Data will be analysed using paired t-tests and analyses of variance. The trial has been approved in the UK by the London City and East Research Ethics Committee (25/PR/0098). The findings from the study will be disseminated through peer-reviewed journals and presentations at national and international scientific conferences. Trial registration number: ISRCTN56375691.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sedentary behaviour increases the risk of all-cause mortality for people with type 1 diabetes (T1D), with suboptimal glucose management implicated as a key contributor to this increased risk. Hybrid closed-loop (HCL) systems have been shown to improve glycaemic management in adults when compared with insulin being administered as multiple daily injections (MDI) or via continuous subcutaneous insulin infusion (CSII). Recent research has demonstrated the effectiveness of breaking up sitting with frequent bouts of low-intensity activity on glucose 'time in range' (TIR). However, the potential benefit of breaking up sitting on TIR is yet to be investigated in people using HCL systems.

INTRODUCTION

Background

Prolonged exposure to hyperglycaemia and glycaemic variability is associated with an increased risk of cardiovascular disease (CVD) in people with type 1 diabetes (T1D).[1 2] Recent evidence suggests that prolonged periods of sedentary behaviour are related to increased HbA1c levels[3] and, in turn, that this behaviour can contribute to an increased risk of CVD. *Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure of ≤1.5 metabolic equivalents while in a sitting, reclining or lying posture,*[4] *of which prolonged sitting is the most common form.* Indeed, prolonged periods of sitting are more prevalent in people with T1D[5] and have been independently associated with increased risk of cardiovascular events and all-cause mortality in T1D.[6]

Given the early onset and high prevalence of CVD in T1D, there is increasing interest in modifiable lifestyle behaviours that can improve glucose management and

For numbered affiliations see end of article.

Correspondence to
Joseph Graham Jenkins; jgj301@student.bham.ac.uk

WHAT THIS STUDY ADDS

⇒ While recent advances in diabetes technologies (ie, HCL systems) have improved glycaemic management, research is yet to assess the glycaemic effects of breaking up sitting in people using HCL systems. This study will be the first to directly assess the glycaemic benefits of breaking up sitting in people using HCL systems, seeking to determine whether frequent, brief bouts of low-intensity activity can provide additional meaningful glycaemic benefit. In addition, this study will be the first to assess potential changes in peripheral and cerebral vascular function in response to breaking up sitting in T1D.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If this study finds that breaking up sitting can improve glucose management and/or vascular function in people with T1D using HCL systems, it will show that frequent, brief bouts of low-intensity physical activity can confer additional cardiovascular and health benefits to the improved glycaemic management already provided to those using HCL systems.

metabolic health. While there is strong evidence that exercise improves cardiovascular health in T1D,[7 8] structured exercise can be challenging due to barriers such as fear of hypoglycaemia, low baseline fitness and time constraints.[9 10] Consequently, there is growing interest in alternative pragmatic and accessible strategies to structured exercise that break up sedentary time and improve glucose management in T1D.[5]

Beyond glucose management, vascular dysfunction is an early and prevalent feature of T1D, occurring independently of traditional cardiovascular risk factors[11] and itself predicting increased CVD risk. [11–13] Notably, sedentary behaviour acutely impairs vascular function, and interrupting sedentary time with brief activity bouts has been shown to attenuate or reverse these impairments in other at-risk populations.[14–16] Whether similar benefits are observed in individuals with T1D using hybrid closed-loop (HCL) systems has not yet been examined.

A promising approach to reducing prolonged sedentary behaviour in T1D involves incorporating brief, frequent bouts of low-intensity physical activity into daily routines.[17] Campbell *et al*[17] reported that interrupting 7 hours of sitting with 3 min bouts of self-paced walking every 30 min increased glucose time in range (TIR; 3.9–10.0 mmol/L) by 13.7% and reduced glycaemic variability by 7.8% over the subsequent 48-hour period, compared with uninterrupted sitting in adults with T1D.[17] Compared with structured exercise, these activity breaks require minimal time commitment, do not rely on specialist equipment or facilities, and can be integrated with relative ease into daily routines, leading to potentially improved adherence.[18] Whether these benefits translate to real-world free-living settings remains to be established but is currently being investigated by our group (EXTOD-Active RCT[19]).

Previous studies in T1D have collected data from individuals either managing their diabetes using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), however it remains unclear whether benefits would be observed in those using the newly developed HCL systems.[17 20] HCL systems, also referred to as an automated insulin delivery system or an 'artificial pancreas', automatically adjust rapid-acting insulin delivery in real-time, based on continuous glucose monitoring (CGM) data, and have been shown to improve glycaemic outcomes compared with MDI or CSII.[21 22] In the UK, HCL systems have been incorporated into the National Institute for Health and Care Excellence (NICE) guidelines, which recommend their use for the majority of individuals with T1D to support optimal glycaemic management.[23] As HCL systems already aim to optimise TIR, the benefits of breaking up sitting on glucose management may be smaller when compared with those benefits observed in participants using MDIs or CSII. However, this remains to be determined.

This study will investigate the acute effects of breaking up prolonged sitting on glycaemic management and vascular function in individuals with T1D using HCL systems. It is hypothesised that interrupting sitting with activity breaks will acutely improve glucose management and enhance both peripheral and cerebral vascular function compared with uninterrupted sitting.

Study aims

The primary aim of this research is to investigate the influence of breaking up 7 hours of prolonged sitting (Sedentary) with scheduled 3 min bouts of self-paced walking every 30 min (Active Breaks) on glucose TIR in adults with T1D who use HCL systems.

Secondary aims of the study include investigating the impact of scheduled Active Breaks on additional markers of glycaemia (as outlined in the most recent consensus[24]), peripheral and cerebral vascular function and blood flow, insulin dose, serum markers of inflammation and blood pressure. The aims, outcome measures and specific time points of evaluation are shown in table 1.

METHODS AND ANALYSES

Trial design

The study will use a randomised, crossover design, in which participants will complete two, 7 hour experimental conditions each separated by at least 4 days. One condition will involve participants sitting uninterrupted for 7 hours (Sedentary), while the other will involve participants breaking up 7 hours of sitting with 3 min of self-paced walking every 30 min (Active Breaks). The current protocol was adapted from that previously described by Campbell *et al*.

The trial protocol adheres to Recommendations for Interventional Trials and the Template for Intervention Description[25] and replication guidelines (TIDieR).[26]

Study setting and recruitment plan

Recruitment of 24 adult men and women with T1D will take place over 18 months, with the trial finishing (last

Table 1 Primary and secondary outcome measures and associated time points of evaluation

Objective	Outcome measures	Evaluation timepoints
Primary objectives		
Time in target glycaemic range	Glucose TIR (3.9–10.0 mmol/L) via CGM	Mean during intervention (0–7 hours) Mean 48 hours postintervention (7–55 hours)
Secondary objectives		
Markers of glycaemia	Mean glucose, time in tight range (3.9–7.8 mmol/L), % time in hypoglycaemia (<3.0 and 3.0–3.9 mmol/L), % time in hyperglycaemia (10.1–13.9 and >13.9 mmol/L), glycaemic variability (CV, SD), hypoglycaemia/hyperglycaemia episodes, area under the curve via CGM	Mean during intervention (0–7 hours) Mean 48 hours postintervention (7–55 hours)
Insulin dose	Insulin log via HCL. Basal, bolus and total units.	Mean during intervention (0–7 hours) Mean 48 hours postintervention (7–55 hours)
Peripheral vascular function	Superficial femoral artery FMD	Change (baseline to postintervention)
Peripheral blood flow	Superficial femoral artery blood flow and shear rate	Change (baseline to postintervention)
Cerebral blood flow	CCA and ICA blood flow	Change (baseline to postintervention)
Cerebral vascular function	Middle cerebral artery blood velocity MCAv and CVR	Change (baseline to postintervention)
Serum markers of inflammation and vascular function	ET-1 concentrations, VCAM-1 concentrations, ICAM-1 concentrations and IL-6 concentrations	Change (baseline to postintervention)
Blood pressure	Resting BP	Change during intervention (0, 1.75, 3.5, 5.25, 7 hours)

BP, blood pressure; CCA, common carotid artery; CGM, continuous glucose monitor; CV, coefficient of variation; CVR, CO_2 reactivity; ET-1, endothelin 1; FMD, flow-mediated dilation; HCL, hybrid closed-loop; ICA, internal carotid artery; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; MCAv, middle cerebral artery blood velocity; TIR, time in range; VCAM-1, vascular cellular adhesion molecule 1.

data collection from the last participant) in July 2027. Testing will take place in laboratories at the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham (UoB), the Research Institute for Sport and Exercise Sciences at Liverpool John Moores University (LJMU) and the Department of Sport and Exercise Sciences at Manchester Metropolitan University (MMU).

Targeted recruitment based on the relevant inclusion/exclusion criteria will use:

1. Clinical database searches, and subsequent recruitment letters sent from the Queen Elizabeth Hospital, Birmingham, for patients with T1D currently using HCL systems.
2. Emails sent to volunteers within the ‘Research for the Future’ consent to approach database.
3. Advertisements on the diabetes UK website through the ‘Take part in research’ portal.
4. Advertisements on the breakthrough T1D website through the ‘T1D research studies’ page.
5. Advertisements through diabetes support groups.
6. Advertisements on social media (eg, Facebook, LinkedIn).
7. UoB, LJMU, MMU staff and students: via advertisements around the campus and internal emails.

Interested potential participants will be invited to contact the research team via email to receive a participant information sheet.

Eligibility criteria

Inclusion criteria

- Having been diagnosed with T1D for more than 3 years.
- Aged 18–66 years.
- Using an HCL system.

Exclusion criteria

- Pregnant or planning to become pregnant.
- <6 months postpartum or stopped breastfeeding <1 month before recruitment.
- Having been diagnosed with cerebrovascular or CVD.
- Having a significant history of uncontrolled hyperglycaemia (HbA1c>85 mmol/L).
- Having a history of severe hypoglycaemia requiring third-party assistance within the last 3 months.

- Acute illness or infection within the last 2 weeks prior to laboratory visit (eg, cold, influenza, COVID).
- Musculoskeletal injury or physical impairment that prevents walking unaided.

Study timeline

Pre-experimental period

A research team member will assess potential participants' eligibility during an initial phone/video call. Those who meet the study's eligibility criteria and remain interested in joining the study will be invited to provide informed consent using the eSignature software DropBox Sign. Should informed consent be provided, participants will complete a study-specific online questionnaire (via Microsoft Forms), asking for their age, sex, ethnicity, height, weight, medical history (including pregnancy, menopausal stage (pre-, peri- or post-menopausal), menopause-related medication use (eg, hormone replacement therapy) and birth control), most recent HbA1c and diabetes history (duration of T1D, hypoglycaemic events within the past 3 months). In addition to the study-specific questionnaire, and 7 days prior to their first laboratory visit, participants will be asked to complete the short form International Physical Activity Questionnaire (IPAQ).[27]

Participants will then be mailed an initialised activPAL4 physical activity monitor (PAL Technologies, Glasgow, UK) along with written instructions and diagrams detailing correct placement on the anterior midline of the thigh, in line with manufacturer guidelines. A member of the research team will also contact participants via phone or video call to confirm correct placement of the monitor before monitoring begins. They will be asked to wear the monitor for 48 hours prior to and for 48 hours following each laboratory visit. Participants will also be asked to record their diet for 48 hours prior to and for 48 hours following each laboratory visit using a mobile app (MyFitnessPal). Data sharing using the participant's own CGM and HCL system will be initiated so that each participant's interstitial glucose and insulin data can be accessed and downloaded. Premenopausal female participants will be tested in the early follicular phase of their menstrual cycle to control for hormonal fluctuations.[28 29] For peri-menopausal participants, where precise cycle phase identification may not be possible due to cycle irregularity, testing will be scheduled at a convenient time and self-reported cycle information and hormone-related medication use will be documented.

The order of the two trial conditions will be randomised and counterbalanced using a computer-generated random allocation sequence (www.randomization.com). Due to the nature of the study, blinding of the participants or researchers is not possible. However, participants and researchers will be blinded to experimental condition order until the morning of the first trial. The analysis and interpretation of the data will also be blinded. See figure 1 for a schematic overview of the study.

Experimental period

At 06:00 hours on the morning of each trial, participants will be instructed to consume a standardised breakfast before being contacted by phone to confirm that their glucose levels are within the range of 3.9–10 mmol/L. The trial will be rearranged if blood glucose concentrations are not within this range or if participants have experienced one or more sustained (>90 min) hyperglycaemic (glucose readings>10 mmol/L) or sustained (>30 min) hypoglycaemic (glucose readings<3.9 mmol/L) episodes

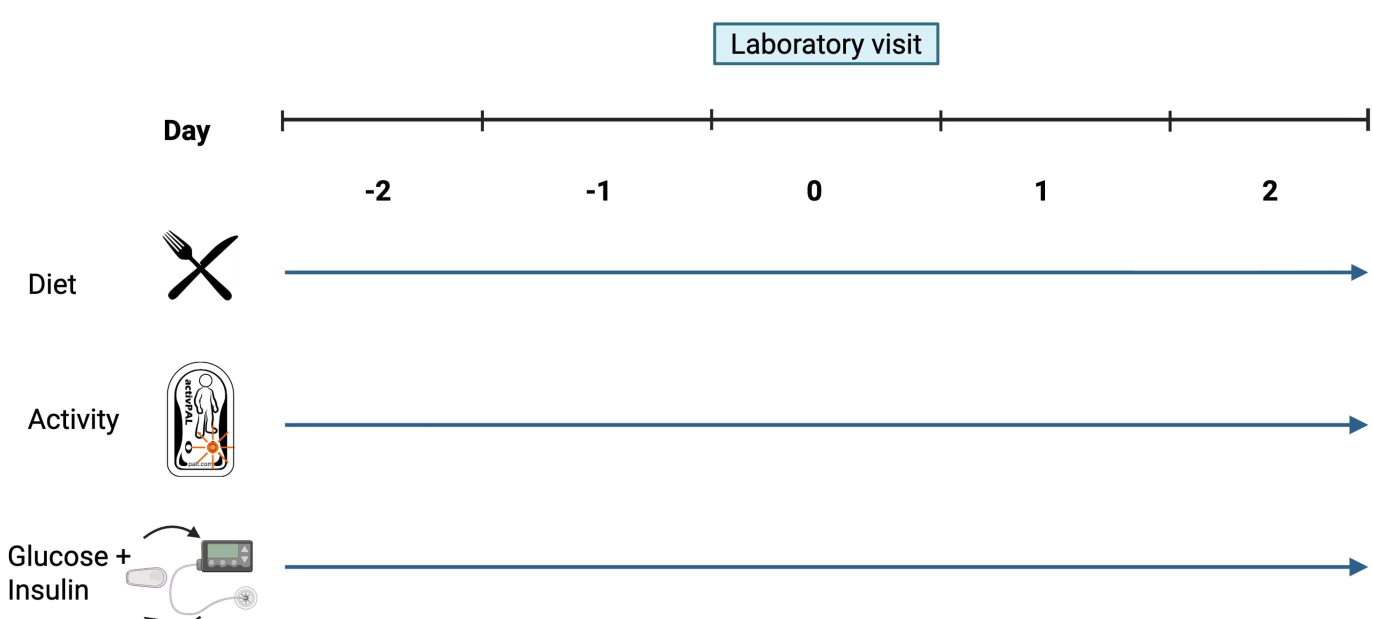

Figure 1 Overview of the study timeline. 48 hours previsit and 48 hours postvisit, participants will record their diet, have their activity monitored (activPAL) and glucose and insulin will be recorded (continuous glucose monitor and hybrid closed-loop system). After >4 days participants will complete the second trial condition.

during the previous 24 hours[30]. Participants will be asked to arrive at the laboratory (avoiding walking or cycling) by 07:30 hours. After arrival, participants will have their height and weight measured before being asked to lie supine—which will start a 60 min 'steady state' baseline assessment period (at 08:00 hours). During the following 60 min, peripheral and cerebral vascular function, in addition to blood sampling and blood pressure, will be assessed in a quiet, dimly-lit, temperature-controlled (22°C–25°C) room adjacent to a workstation where participants will be seated for each trial. Following the baseline assessment, participants will be seated at the workstation in an upright chair ready to begin the intervention (09:00 hours). While seated, participants will be encouraged to keep their feet flat on the ground, with their legs uncrossed. Lower body movements and bathroom breaks will be allowed to replicate free-living conditions. Participants will have access to the internet and will be able to work, read, etc. Water will be provided ad libitum. At 12:30 hours, a standardised lunch will be provided. Food intake before and after lunch will be restricted unless required to treat hypoglycaemia (blood glucose <3.9 mmol/L). Seated, resting blood pressure measurements will be taken every 1.75 hours for a total of five measurements throughout the day.

During the Active Breaks condition, participants will break up their sitting every 30 min with supervised 3 min bouts of self-paced walking. The walking will be prescribed as low-intensity and timed to occur every 30 min with the first Active Break beginning at 09:30 hours and the final one finishing at 16:03 hours. During the Sedentary condition, participants will be supervised while they remain seated for 7 hours.

On completion of each 7 hour condition, participants will once again lie supine to begin the post-testing measures. Following the completion of these measures, participants will be permitted to leave the laboratory (17:00 hours). Each will continue to wear their physical activity monitor and to record their diet for an additional 48 hours. After leaving the laboratory, participants will be instructed to consume a standardised dinner at 19:00 hours. At least 4 days will separate the two conditions. Figure 2 shows the laboratory visits with associated measurements and timepoints.

Standardisation of diet and insulin administration

For each condition, participants will receive four standardised, mixed-macronutrient meals designed to meet total estimated energy requirements based on the Schofield equation (physical activity level=1.5), with breakfast, lunch and dinner each providing 33.3% of total energy. Meals will be matched for macronutrient content as a percentage of total calories. The precondition dinner and breakfast will be prepackaged and home-delivered using a delivery service on the days leading up to each lab visit, with instructions provided on when to consume

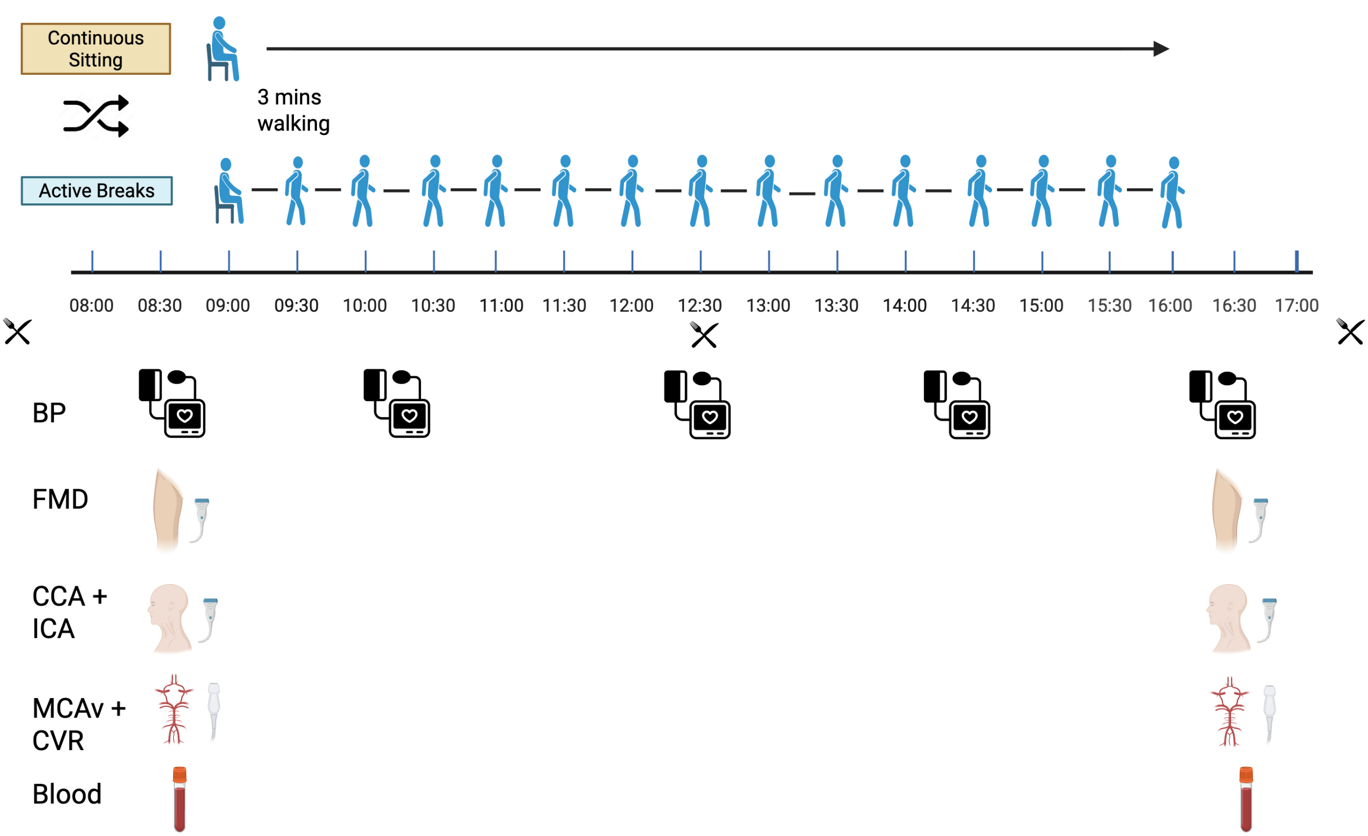

Figure 2 Laboratory visit schematic with associated measurements and timepoints. BP, blood pressure; CCA, common carotid artery; CVR, CO_2 reactivity; FMD, flow-mediated dilation; ICA, internal carotid artery; MCAv, middle cerebral artery velocity.

each meal. Participants will be provided with the carbohydrate content for each meal and will bolus for all meals using the pump's bolus calculator, the timing of which will be replicated across visits.

Outcome measures

Blood glucose (interstitial glucose via continuous glucose monitoring)

Participants will continue to use their own clinically approved CGM device compatible with their HCL system for the duration of the study. This includes, but is not limited to, Abbott FreeStyle Libre (2+ or 3) (Abbott Diabetes Care, UK), Dexcom (G6 or G7) (Dexcom, San Diego, CA, USA) or Medtronic (Guardian 3 or 4) (Medtronic, Northridge, CA, USA) devices. The trial periods will be timed to begin when a new sensor is inserted and initialised. The research team will request access to participants' glucose reports using their respective devices' online data-sharing platforms, and this will enable the research team to access glucose data using proprietary software (LibreView, Dexcom Clarity, Glooko, CareLink). Where platform access to glucose data is not possible, participants will be asked to provide a downloaded report or log of glucose data directly. Glucose data will be accessed 48 hours prior to the first laboratory visit and for 48 hours following the final visit. After this time, the research team will download the data and cease using the remote data-sharing link.

Insulin (insulin pump)

Participants will continue to use their own HCL insulin pump for the duration of the study. This includes but is not limited to, Medtronic 780G, Tandem T:Slim (Tandem Diabetes Care, San Diego, CA, USA), Dana Diabecare RS, Dana-I (Sooil Development Co, Seoul, Korea), Ypsopump (Ypsomed AG, Burgdorf, Switzerland) or Omnipod 5 (Insulet Corporation, Acton, MA, USA) pumps. The research team will request access to participants' insulin data using their respective devices' online data-sharing platforms; this will enable the research team to view and download current and historical insulin data using proprietary software (CareLink, Tandem Source, Dana Manager, Glooko). Data on basal, bolus insulin infusion units will be obtained. Insulin data will be accessed 48 hours prior to the first laboratory visit and for 48 hours following the final visit. Where platform access to insulin data is not possible, participants will be asked to provide a downloaded report or log of basal and bolus insulin units directly. Following the trials, the research team will download the data and cease using the remote data-sharing link.

Peripheral vascular function (superficial femoral artery flow-mediated dilation and blood flow)

Peripheral conduit arteries such as the superficial femoral artery have been found to be largely mediated by nitric oxide, therefore reflecting endothelium-dependent vascular function.[31] A rapid inflation and deflation pneumatic cuff (Moor Instruments, Axminster, UK) will be positioned distal to the knee joint (2–3 cm from the patella) on the right leg.[32] Following 20 min of supine rest, the superficial femoral artery will then be located using a 10-MHz multifrequency linear array probe in conjunction with high-resolution duplex ultrasound (Terason t3300, Teratech, Burlington, MA). Once an optimal image of the artery is obtained, the ultrasound transducer will be held at the site of measurement and data will be recorded onto a laptop using a video capture device (Cardiovascular Suite, Quipu S.r.l., Pisa, Italy). A recording of continuous resting vessel diameter and blood velocity will be measured initially for 1 min to capture baseline measurements. The cuff will then be inflated (~220 mm Hg) for 5 min, following which the cuff will be deflated (<2 s), and blood flow will return; ultrasound recordings will continue for a further 5 min to assess the postdeflation arterial diameter and peak blood velocity. Placement of the probe will be marked and recorded on the first scan and replicated for the second. Recordings will be captured and saved for offline analysis using edge-detection and wall-tracking software (Cardiovascular Suite, Quipu S.r.l., Pisa, Italy). All file images will be analysed by the same trained researcher. Peak arterial diameter will be defined as the largest diameter post-deflation. The FMD response will be calculated as the maximal percent change in arterial diameter postdeflation relative to preinflation baseline (average diameter recorded during the minute baseline). Blood flow will be calculated by multiplying the cross-sectional area×60 (to convert mL/s to mL/min). Shear rate will be calculated as four times the mean blood velocity divided by the vessel diameter (s^{-1}). To ensure consistency of assessment across all three data collection sites (UoB, LJMU, MMU), all FMD measurements will be conducted by the same trained researcher (JGJ), using the same ultrasound equipment (Terason t3300, Teratech, Burlington, MA) at each site.

Resting cerebral blood flow (common carotid artery and internal carotid artery)

Previous research has demonstrated 75% of global cerebral blood flow is supplied via the internal carotid artery (ICA).[33] To assess cerebral blood flow, participants will remain supine following the FMD measurement while the right common carotid artery (CCA) and right ICA (1.0–1.5 cm distal to the carotid bifurcation) are identified using the same 10-MHz multifrequency linear array probe in conjunction with high-resolution duplex ultrasound. Once optimal images are obtained, the ultrasound transducer will be held at the site of measurement and data will be recorded onto a laptop using a video capture device. First, the CCA will be identified, and blood flow will be averaged over a period of 2 min, followed by the ICA. Recordings will be saved for offline analysis using edge-detection and wall-tracking software (Cardiovascular Suite). All file images will be analysed by the same trained researcher, blinded to condition. The average blood flow of both vessels will be calculated using the mean vessel diameter and flow velocity across the 2 min of recording.[34 35] The time-averaged mean flow velocity will be obtained using the pulse-wave mode, defined as the mean blood flow velocity (cm/s). Blood flow will be calculated by multiplying the cross-sectional area × 60 (to convert mL/s to mL/min).

Cerebral vascular function (middle cerebral artery velocity)

Middle cerebral artery velocity (MCAv) will be used as a surrogate measure for cerebral blood flow.[36] Continuous bilateral transcranial Doppler ultrasound (TCD) (DopplerBox, DWL, Compumedics Ltd, Germany; ST3; Spencer Technologies, Redmond, WA; WAKI; Atys Medical, St Genis Laval, France) will be used to measure the left and right MCAv. Participants will be seated while a 2-MHz Doppler probe is positioned over the temporal window and is secured using an adjustable headband. Each MCA will be identified based on the signal depth, peak and mean blood velocity as previously described.[37] Once optimal signals have been obtained, the probes will be secured in position, and the signal parameters will be noted to ensure within-subject consistency between tests. MCAv data will be recorded using an analog-to-digital converter (Powerlab, ADInstruments, New Zealand) and stored for later analysis. Mean MCAv will be calculated from the mean of the waveform.

Cerebral vascular function (CO_2 reactivity)

Participants will be fitted with a face mask with a two-way non-rebreathing valve (MLA1028; ADInstruments). A Douglas bag filled with a 5% CO_2 mixture and fitted with a three-way valve will enable the breathing circuit to be alternated between ambient air and a 5% CO_2 (in air) mixture. Breath-by-breath CO_2 will be sampled using a calibrated gas analyser (Ml206; ADInstruments), and the pressure of end-tidal CO_2 will be calculated using LabChart software (V. 7.0; ADInstruments). Following a 3 min resting baseline period, participants will breathe from the Douglas bag for 4 min before returning to breathing ambient room air. Participants will then be coached through a mild hyperventilation protocol so that end-tidal CO_2 is reduced to 30 mm Hg. Participants will maintain this hypocapnia for ~30 s.

Beat-by-beat MCAv and blood pressure (measured continuously at the index finger using a Finapres device; Finapres Medical Systems BV, Amsterdam, the Netherlands) along with breath-by-breath respiratory rate and volume and end-tidal CO_2 partial pressure will be continuously measured during the hyper- and hypocapnic protocols. Beat-by-beat MCAv will be calculated as the mean across each cardiac cycle and exported as second-by-second data for analysis.

Baseline values will be averaged over 1 min during the supine rest. CO_2 reactivity (CVR) will be calculated as both absolute (cm/s) and relative (percentage) change from baseline in MCAv per mm Hg change in end-tidal CO_2. The CVR responses will be analysed at established steady state timepoints—the final 30 s of mins 3 and 4—and dynamically, based on the individual's reactivity.[38 39] This analysis will be done independently for both left-sided and right-sided MCA. Ventilation sensitivity will also be calculated within the same timepoints above for both steady state and dynamic responses.

Markers of inflammation (blood sampling and serum concentrations)

Venous whole blood (3 mL) will be sampled from an antecubital vein into EDTA tubes and will be centrifuged within 5 min of collection; the plasma will then be stored at −80 °C until the later analysis of endothelin 1 (ET-1), vascular cellular adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and interleukin 6 (IL-6) concentrations. All blood markers will be assessed using validated ELISA kits.

Blood pressure

Seated resting blood pressure will be measured using a digital sphygmomanometer (Omron M2, Omron Healthcare Co, Kyoto, Japan).

Study withdrawal

Participants will have the right to withdraw from the study at any time, with no obligation to provide a reason. If provided, reasons for withdrawal will be retained, but personal data will be deleted. In addition, participants may be withdrawn from the study by the research team at any time should there be significant safety concerns. Withdrawal from the study will not necessarily exclude a participant's data from analysis.

Data analysis

Sample size

Based on previously published data in adults using HCL systems, a power calculation has shown that 19 participants will be required to detect a 5% difference in TIR. Calculations are based on a power of 90% and an α of 0.05, assuming an SD for TIR of 6.3%.[40] To account for the potential dropout of 20%, 24 participants will be recruited (G*Power V.3.1.9.6).

Markers of glycaemia

Glucose metrics will be calculated according to international consensus guidelines for CGM data analysis: mean glucose concentration, TIR (3.9–10.0 mmol/L), time in tight range (3.9–7.8 mmol/L), time in level 1 hypoglycaemia (3.0–3.8 mmol/L), time in level 2 hypoglycaemia (<3.0 mmol/L), time in level 1 hyperglycaemia (10.1–13.9 mmol/L), time in level 2 hyperglycaemia (>13.9 mmol/L), glycaemic variability (coefficient of variation (CV) and SD), number of hypoglycaemic episodes (defined as glucose <3.9 mmol/L for a duration of ≥15 min), hyperglycaemic episodes (defined as glucose >10.0 mmol/L for a duration of ≥15 min) and area under the curve for hypoglycaemic and hyperglycaemic excursions. All glucose data will be processed using a CGM analysis software.[41]

Statistical analyses

The primary outcome will be glucose TIR during the intervention (0–7 hours) and across the 48-hour postintervention period (7–55 hours). Secondary outcomes will include additional markers of glycaemia (mean glucose, time in tight range, time in hypoglycaemia and hyperglycaemia, glycaemic variability, episode counts and area under the curve), vascular and cerebrovascular measures (superficial femoral artery flow-mediated dilation, blood flow and shear rate, CCA and ICA blood flow, middle cerebral artery blood velocity and CVR), serum markers of vascular function and inflammation (ET-1, VCAM-1, ICAM-1, IL-6) and insulin dose. For outcomes with baseline and post-testing measurements, change scores (Δ=post–baseline) will be calculated. For each outcome, within-participant differences between conditions (Active Breaks vs Sedentary) will be assessed using paired samples t-tests. Results will be presented as mean±SD and 95% CI, with α=0.05. If data violate normality assumptions, non-parametric equivalents (Wilcoxon signed-rank tests) will be used.

Resting blood pressure (systolic, diastolic and mean arterial) will be analysed separately using a two-way repeated-measures analysis of variance (ANOVA) with factors of Condition (Active Breaks vs Sedentary) and Time (T1–T5), with the Time×Condition interaction as the primary effect of interest. Where baseline differences between conditions are significant, baseline values will be included as a covariate.

All analyses will be two-tailed with α=0.05 and performed using SPSS (V.29).

Physical activity data

Physical activity data will be processed and analysed using PALanalysis software (PAL Technologies, Glasgow, UK), providing outputs including daily step count, sit-to-stand transitions and time spent sitting, standing and stepping, to determine whether differences exist between conditions across the 48 hours prior to, during and 48 hours following each laboratory visit. Outcomes will include total daily steps, sit-to-stand transitions, time spent walking or sitting and sedentary time accumulated in bouts >30 and >60 min. Data will be analysed using a two-way repeated-measures ANOVA with factors of Condition (Active Breaks vs Sedentary) and Time (−48 hours, visit day, +48 hours). The Condition×Time interaction will represent the main effect of interest. Where sphericity is violated, Greenhouse–Geisser corrections will be applied. Non-normally distributed variables will be log-transformed, and all results will be expressed as mean±SD with a 95% CI.

Participant demographics and questionnaire data

Participant characteristics and baseline questionnaire data (eg, age, sex, diabetes duration, HbA1c and self-reported physical activity) will be summarised using descriptive statistics, presented as mean±SD for continuous variables and frequency (percentage) for categorical variables.

Ethics

The trial protocol has received favourable opinion from the London City and East Research Ethics Committee (25/PR/0098).

Dissemination

On completion of the study, the data will be analysed, and results will be disseminated via publication in clinical and physiological journals, presented at national and international conferences, and in the form of participant feedback sheets. Participants will not be identifiable from the results of the study.

Serious adverse events reporting

Patients will be asked if an adverse event (AE) has occurred during meetings held post-testing. Should an AE be reported, the study's lead clinicians Dr Rob Andrews and Dr Parth Narendran will assess the event and the end outcome using a Serious Adverse Events Report Form. The research team will then report the event to the sponsor.

Author affiliations
[1]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
[2]Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK
[3]Department of Sport and Exercise Sciences, Manchester Metropolitan University, Manchester, UK
[4]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[5]Institute for Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
[6]Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK
[7]Sestante Analytics AG, Bern, Switzerland

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ORCID iDs
Joseph Graham Jenkins https://orcid.org/0009-0007-1365-4862
Samuel J E Lucas https://orcid.org/0000-0002-8713-2457
Jacob Harrison Tennant https://orcid.org/0009-0008-2133-8859

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