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TITLE: Interrupting prolonged sitting with frequent short bouts of light-intensity activity in people with type 1 diabetes improves glycaemic control without increasing hypoglycaemia: The SIT-LESS randomized controlled trial

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ABSTRACT

Aims: To examine the impact of interrupting prolonged sitting with frequent short bouts of light-intensity activity on glycaemic control in people with type 1 diabetes (T1D).

Materials and methods: 32 inactive adults with T1D (aged 27.9±4.7 years, 15 men, diabetes duration 16.0±6.9 years and HbA1c 8.4±1.4% [68±2.3 mmol/mol]) underwent two 7-hour experimental conditions in a randomised crossover fashion with >7-day washout consisting of: uninterrupted sitting (**SIT**), or, interrupted sitting with 3-minute bouts of self-paced walking at 30-minute intervals (**SIT-LESS**). Standardised mixed-macronutrient meals were administered 3.5-hours apart during each condition. Blinded continuous glucose monitoring (CGM) captured interstitial glucose responses during the 7-hour experimental period and for a further 48-hours under free-living conditions.

Results: SIT-LESS reduced total mean glucose (**SIT** 8.2±2.6 vs. **SIT-LESS** 6.9±1.7 mmol/L, P=0.001) and increased Time in Range (TIR; 3.9-10.0 mmol/L) by 13.7% (**SIT** 71.5±9.5 vs. **SIT-LESS** 85.1±7.1 %, P=0.002). Hyperglycaemia (>10.0 mmol/L) was reduced by 15.0% under **SIT-LESS** (**SIT** 24.2±10.8 vs. **SIT-LESS** 9.2±6.4 %, P=0.002), whereas hypoglycaemia exposure (<3.9 mmol/L) (**SIT** 4.6±3.0 vs. **SIT-LESS** 6.0±6.0 %, P=0.583) was comparable across conditions. **SIT-LESS** reduced glycaemic variability (CV%) by 7.8% across the observation window (P=0.021). These findings were consistent when assessing discrete time periods, with **SIT-LESS** improving experimental and free-living postprandial, whole-day, and night-time glycaemic outcomes (P<0.05).

Conclusions: Interrupting prolonged sitting with frequent short bouts of light-intensity activity improves acute postprandial and 48-hour glycaemia in adults with T1D. This pragmatic strategy is an efficacious approach to reducing sedentariness and increasing physical activity levels without increasing risk of hypoglycaemia in T1D.

Clinical Trial Registry Number: ISRCTN13641847

INTRODUCTION

Physical activity is a critical element of diabetes care and is universally recommended to all individuals with diabetes[1]. Recently, guidelines have evolved to stipulate that in addition to traditional structured moderate-vigorous intensity physical activity, individuals should limit prolonged periods of sitting by incorporating frequent episodes of low-intensity physical activity into the day[2]. This recommendation is based upon data demonstrating a dose-dependent relationship between sedentary behaviour and cardiometabolic morbidity, worsening glycaemic management, and increased weight gain, irrespective of physical activity status[3,4]. Further, emerging evidence demonstrates that interruption of prolonged sitting with frequent short bouts of activity improves acute postprandial and whole-day glucose levels, with glycaemic improvement continuing until the next morning[5-9], resulting from enhanced contraction-induced and/or energy deficit-induced insulin sensitivity[31], and/or a greater reliance on insulin-independent contraction-mediated glucose disposal[32]. However, these data remain preliminary and limited to individuals with, or at risk of developing, type 2 diabetes.

Within the context of type 1 diabetes (T1D), most individuals struggle to meet physical activity guidelines[10] and spend a greater proportion of time sedentary than people without T1D[11]. For example, a recent large cross-sectional survey of 18,028 adults with T1D, reported that ~60% did not achieve recommended physical activity levels[10] a finding which supports some[12-14], but not all previous studies[15].

Many people with T1D report fear of hypoglycaemia and an inability to manage their diabetes as major barriers to becoming active and engaging in regular moderate-to-vigorous physical activity participation[14], yet, few mention this fear when asked about lower-intensity activities such as walking[16]. although many individuals with T1D do little-to-no exercise, they are often willing to increase participation in lower-intensity physical activity and are keen to learn how to reduce sedentary behaviours[14,16,17]. However, little information is available for individuals with T1D or for the healthcare professionals who support them with regards to strategies for reducing sedentariness and their potential impact on hypoglycaemia risk[14,16,17].

Should findings from recent research in individuals with type 2 diabetes translate to those with T1D, interrupting sitting with frequent, short, light-intensity activity breaks, may serve as a pragmatic strategy for enabling inactive T1D individuals to incorporate more physical activity into their everyday lives and improve glucose management. This may be particularly beneficial

for those who are unable or unwilling to engage in structured moderate-vigorous physical activity and an important stepping-stone towards achieving physical activity recommendations. However, no research has investigated the impact of such a strategy on glucose control in people with T1D. Therefore, the aim of this study was to examine the acute postprandial and subsequent 48-hour free-living glucose responses to interrupting prolonged sitting with frequent, short bouts of light-intensity activity in inactive people with T1D.

METHODS

Study Design

This randomised crossover trial was undertaken at the University of Sunderland between May 2021 and December 2022. The study received ethical approval from the Health Research Authority (HRA; London – Surrey Research Ethics Committee; Ref 20/LO/0650) and was prospectively registered (ISRCTN13641847). All patients who participated provided written informed consent with study procedures complying with the Declaration of Helsinki. Participants completed an initial medical screening visit and two laboratory-based experimental visits each of which were separated by a minimum of 7 days (Supplementary Figure 1). Experimental conditions were randomly assigned using a computerized random number generator (www.randomization.com) with study personnel and participants blinded to experimental condition order up until commencement of the first experimental visit.

Participants

Patients with autoantibody confirmed T1D treated on a stable (>6 months) insulin regimen consisting of continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDIs) were recruited in-clinic and via university recruitment streams from the North-East region of the United Kingdom. Patients were eligible for inclusion if aged between 18 and 60 years with a duration of diabetes >2 years on enrolment and classified as inactive as per international physical activity guidelines[1,2]; specifically, this consisted of failing to achieve a minimum of 150 minute of moderate-vigorous intensity physical activity per week. Pregnancy, the presence of significant functional limitations, dietary intolerances, overt diabetes complications, or hypoglycaemia unawareness – as determined by the Clarke method[18] – were exclusion criteria.

Pre-experimental procedures

After initial telephone screening, potentially eligible participants underwent medical screening at our laboratory for assessment of pre-treatment clinical characteristics including medical history, anthropometry, blood pressure, and self-reported physical activity status using a validated assessment tool[19]. During this visit eligible participants then underwent initial study orientation and were fitted with a blinded continuous glucose monitoring (CGM) device (FreeStyle Libre Pro iQ, Abbott, UK). Participants were provided with a food diary to record diet and insulin regimen and were provided with a pedometer to which recorded total step count during each 24-hour period of the 48-hours before and after the first experimental laboratory visit; this information was then used to replicate diet, insulin administration and physical activity levels during the second experimental period. During this time, participants were required to abstain from exercise, caffeine, and alcohol in the 48-hours prior to each experimental condition. Prearranged, standardized text messaging and/or email prompts were used to maximize participant compliance.

For standardisation of glycaemic control prior to each laboratory visit, a standardised mixed-macronutrient meal (Supplementary Table 1) was provided to participants to consume on the evening before each experimental visit; following consumption of this meal, participants were instructed to avoid further food intake including calorific beverages, except for extremes of glucose readings managed as appropriate with corrective insulin boluses for hyperglycaemia and glucose supplementation for hypoglycaemia. The aim was to ensure fasting status upon arrival to each experimental visit as detailed below. On the morning of each experimental visit, study personnel contacted participants to ensure fasting status and confirm glucose levels were within the range 4-12 mmol/L. Experimental visits were re-arranged if participants experienced one or more sustained (>90-minutes) hyperglycaemic or sustained (>30 minute) hypoglycaemic episodes. To limit the potential impact of menses on glycaemic measures for menstruating female participants, procedures were arranged to occur within two-consecutive weeks during their follicular phase (self-reported).

Experimental procedures

A schematic of the experimental procedures is presented in Supplementary Figure 1. Participants attended our temperature-controlled (21-23°C) laboratory on a morning (~08:00) following an overnight fast. On both occasions participants consumed standardized mixed-macronutrient breakfast and lunch meals at 3.5-hours apart with start time equivalent on both

experimental arms. Each meal sought to replicate a typical Western diet with an energy density of ~855 kcal, and a macronutrient profile of ~42% energy from carbohydrate, ~16% energy from protein, and ~42% energy from fat (Supplementary Table 1). The carbohydrate content of each meal was individualized equating to 1g carbohydrate per kilogram body mass. Participants were instructed to administer their usual prandial insulin bolus immediately prior to each meal, the dose of which was calculated using an individuals' established insulin-to-carbohydrate ratio, with dose, timing and site of injection replicated across visits. Water was consumed ad libitum during the first visit with the volume recorded and replicated during visit two; standardized (within subject) lavatory visits were incorporated into the protocol to minimize unscheduled physical activity; however additional lavatory visits were permitted if needed. On one arm (**SIT**), participants remained at rest and seated in a reclining chair for the duration of the visit. On a second arm (**SIT-LESS**) study procedures were replicated but sitting was interrupted by performing 3-minute bouts of self-paced light-intensity walking at 30-minute intervals, commencing 60-minutes after each meal; this equated to a total of 36-minutes of physical activity across the 7-hour period. During each laboratory visit, participants had access to television, books, and internet, and were supervised consistently by study personnel to ensure resting periods were maintained. At 3.5-hours post-lunch, participants were discharged from the laboratory with further free-living glycaemic assessment captured remotely via CGM for a further 48-hours. To minimize potential confounding of food intake, participants were provided with an evening and breakfast meal to consume in sequence, replicating eating times within each study arm (Supplementary Figure 1). Any additional nutritional intake during the subsequent 48-hour observation window was recorded on visit one, and subsequently replicated on visit two. All meals provided to the participants consisted of commercially available foods with standardized heating and preparation instructions. During the >7-day washout between experimental conditions, participants resumed their habitual diet and physical activity patterns, excluding the 48-hours pre-experimental period prior to the next experimental visit.

Continuous Glucose Monitoring (CGM)

Blinded CGM was used to capture interstitial glucose concentrations with sensor insertion a minimum of 72-hours prior to each data capture window to minimize artifacts during initialization. Sensors were inserted into the subcutaneous tissue on the back of the upper arm with insertion site marked with indelible ink to replicate senor insertion site during sensor replacement; existing CGM users continued to use their CGM as normal but were provided with a study-prescribed CGM to ensure consistency in CGM data capture. Data were

retrospectively downloaded and analyzed using manufacturer software (FreeStyle Libre software version 3.12; https://www.libreview.com) with the criterion of >80% data capture within each 24-hour period across each experimental observation window (~5 days on each study arm) with no more than two consecutive hours of missing data during each 24-hour period to be considered valid[20]. From downloaded data, mean glucose, percentage of time in range (TIR: 3.9-10.0mmol/L), time above range (TAR:>10.0 mmol/L and >13.9 mmol/L), and time below range (TBR: <3.9 mmol/L and <3.0 mmol/L), and glycaemic variability (CV%) were calculated as per international guidelines for the use of CGM in clinical trials [20,21].

Data analysis

The primary outcome was 48-hour glycaemic control as assessed by mean glucose. We estimated that 32 paired observations would be required to achieve 95% power to detect a 1.6mmol/L between group difference in mean glucose with an SD of 1.5mmol/L (moderate effect size; Cohen $d = 0.64$) in the primary outcome variable. Our post-hoc power assessment confirmed that our sample size was sufficient to achieve a minimum statistical power of 80% across our secondary outcomes (TIR, TAB, TBR, glycaemic variability). Across both conditions, a total of 26,368 individual CGM derived glucose readings over a combined total of 10 days were analysed, with missing data accounting for <1% (211 of 26,368). CGM data were summarised into three periods: (1) 48-hour pre-experimental phase, (2) experimental phase, and (3) 48-hour post-experimental free-living phase. The 48-hour post-experimental free-living phase was further summarised into free-living day time periods (awake time: 08:00-23:00), and night-time periods (sleep time: 23:00-08:00).

We employed a series of generalized linear mixed models with random intercepts and Bonferroni-corrected *post-hoc* pairwise comparisons to evaluate the differential effects of **SIT** versus **SITLESS** on acute postprandial and 48-hour mean glucose, TIR, TBR, and TAR, as well as glycaemic variability (CV%). Linear regression analyses were utilised to examine potential relationships between pre-treatment clinical characteristics (age, sex, BMI, HbA1c, residual C-peptide, diabetes duration, and treatment regimen (CSII vs. MDI) and the magnitude of treatment response across CGM metrics. Dietary intake, insulin administration, and physical activity (total step count) were summarised for each 24-hour period within the 48-hour post-intervention period and assessed for conditional differences over time using repeated measures ANOVA. To assess mealtime glucose exposure, we calculated net incremental area under the curve (net iAUC) as previously reported[22]. Statistical analyses were performed using SPSS

software (IBM Statistics, version 28), with statistical significance accepted at a threshold of $P \leq 0.05$ and residuals examined for serial correlation, heteroscedascity, and normality. Data are presented as mean±SD unless stated otherwise.

Role of the funding source

This study was funded by Diabetes UK (project grant: 20/0006154). The funder was not involved in the design of the study, data collection, analysis, or interpretation.

RESULTS

Thirty-two participants with T1D (age 27.9±4.7 years, 15/17 males/females, body mass index (BMI) 26.5±3.5 kg/m^2, diabetes duration 16.0±6.9 years, HbA1c 8.4±1.4% [68±2 mmol/mol], CSII:MDI n=15:17) were randomised and completed both experimental conditions (Supplementary Figure 2). Patients displayed similar glycaemic control across the 48-hours preceding each laboratory visit (Table 1), with similar mean glucose (**SIT** 7.7±1.1 vs. **SITLESS** 7.5±2.1 mmol/L; P=0.631), and TIR (3.9-10.0 mmol/L; **SIT** 79.1±12.5 vs. **SITLESS** 81.1±19.9 %; P=0.561). Exposure to hyperglycaemia and hypoglycaemia were also comparable across conditions (P>0.01; Supplementary Table 1). Two patients re-arranged their visits due to hypoglycaemia. Dietary intake, insulin regimen, and physical activity levels were also similar across conditions (P>0.05).

Glucose concentrations at experimental start time were comparable between conditions (**SIT** 7.3±1.5 vs. **SIT-LESS** 7.2±1.8 mmol/L, P=0.774; Figure 1). During the laboratory phase, **SIT-LESS** attenuated postprandial glucose responses following administration of the breakfast (net iAUC: **SIT** 1690±597 vs. **SIT-LESS** 1329±420 mmol/L.min P<0.001) and lunch (net iAUC: **SIT** 1754±735 vs. **SIT-LESS** 1557±558 mmol/L.min P=0.001) test meals, resulting in lower mean glucose (**SIT** 8.5±2.0 vs. **SIT-LESS** 7.1±1.8 mmol/L, P=0.008; Figure 1 and Table 1) and increased TIR by 17% (3.9-10.0 mmol/L; **SIT** 71.6±19.3 vs. **SIT-LESS** 84.6±14.8 %, P=0.004; Table 1) as a consequence of reduced hyperglycaemia (TAR <10.1mmol/L: **SIT** 26.5±27.5 vs. **SIT-LESS** 8.6±18.3 %, P=0.005; Table 1); exposure to hypoglycaemia remained comparable across conditions, irrespective of pre-treatment HbA1c, with similar TBR (<3.9mmol/L: **SIT** 2.7±8.4 vs. **SIT-LESS** 3.34±10.2 %, P=0.795; Table 1) and total number of hypoglycaemic episodes at a threshold of 3.9 mmol/L (**SIT** 4 vs. **SIT-LESS** 5).

***** INSERT FIGURE 1 *****

The glycaemic lowering impact of **SIT-LESS** continued into the free-living period (Figure 1 and Table 1), with lower subsequent 48-hour mean glucose under **SIT-LESS** (**SIT** 8.1±1.3 vs. **SIT-LESS** 6.9±1.5 mmol/L, P=0.001) and increased TIR by 13.0% (**SIT** 71.6±19.3 vs. **SIT-LESS** 84.6±14.8 %, P=0.004). TAR (>10.0 mmol/L) was reduced by 14.4% under **SIT-LESS** (**SIT** 23.8±18.6 vs. **SIT-LESS** 9.4±11.6 %, P=0.001), with TBR (<3.9 mmol/L) comparable across conditions (**SIT** 4.6±5.0 vs. **SIT-LESS** 6.0±9.9 %, P=0.529). **SIT-LESS** reduced 48-hour glycaemic variability (CV%) by 7.2% (P=0.035). These findings were consistent when assessing discrete time periods with **SIT-LESS** improving postprandial, whole-day, and night-time TIR (P<0.05; Figure 1 and Table 1). Dietary intake, insulin administration, and objectively assessed physical activity levels were similar across conditions during the subsequent 48-hour free-living period (P<0.05; Supplementary Table 2).

A significant HbA1c-by-condition interaction effect (P=0.007, F=8.635, η^2=0.249, β=-0.801), and BMI-by-condition interaction effect (P=0.030, F=5.293, η^2=0.169, β=-0.773) were observed for the magnitude of change between **SIT** and **SIT-LESS** in mean glucose. Higher pre-treatment HbA1c and BMI were associated with greater improvements across mean glucose, TIR, TAR, and TBR, but not glycaemic variability (Figure 2; Table 2). Age, sex, diabetes duration, residual C-peptide, and treatment regimen (CSII vs. MDI), did not significantly mediate any of the responses observed (P>0.05).

***** INSERT FIGURE 2 *****

DISCUSSION

This study is the first to evaluate the impact of interrupting prolonged sitting with frequent short bouts of light-intensity activity on glucose control in people with T1D. This intervention improved acute postprandial glucose control, reducing mean glucose concentrations, improving TIR whilst reducing glycaemic variability without increasing exposure to hypoglycaemia. Glycaemic improvement was sustained for at least 48-hours under free-living conditions. Overall, these findings build on previous experimental work in people with or at risk of type 2 diabetes, and support the extension of current physical activity guidelines[2] to individuals with T1D, specifically regarding the interruption of prolonged sitting with frequent, short-duration, light-intensity activity breaks.

In people with diabetes, prolonged uninterrupted sitting is associated with worsening glucose control and increased weight[4,23] which collectively and independently predict both macro- and microvascular complications[24,25]. In the present study, we show that simply interrupting prolonged sitting with regular light-intensity activity breaks results in a net glucose lowering effect of ~1.3mmol/L, with the greatest level of improvements in those with higher pre-treatment HbA1c and BMI. This clinically relevant margin, which if maintained over the long-term, has previously been shown to result in a reduction of HbA1c of ~2%[26], translating to a 38% reduced risk of a macrovascular event, a 40% reduced risk of a microvascular event, and a 38% reduced risk of premature mortality at a HbA1c threshold of 7% or higher[27]; this is substantial given recent data indicating that fewer than 30% of people with T1D achieve the HbA1c treatment target of <7.5%[28].

Importantly, glucose lowering was achieved without increasing the risk of hypoglycaemia. We, and others, have previously shown that moderate-vigorous physical activity predisposes to an increased risk of hypoglycaemia during, immediately following, and late after moderate-vigorous intensity exercise[1], and, that fear of exercise-induced hypoglycaemia is a major barrier to regular participation in physical activity[14]. Whereas exercise is often viewed as daunting and unachievable by many patients, translation of our data into clinical practice and patient education may help to reduce fear of hypoglycaemia surrounding physical activity and enable better glycaemic control when adopting lower-intensity activities. In addition, it is likely that the adoption of our strategy to target sedentary time with short-duration light-intensity activity breaks may serve as a logical starting point for inactive individuals with T1D to develop and build upon achievable and positive behavioural routines that increase overall physical activity levels.

The assessment of acute postprandial glucose control provides novel insightful data. We observed a ~17% improvement in TIR under **SIT-LESS**, resulting almost exclusively from a reduction in hyperglycaemia. Moreover, 75% of patients under **SIT-LESS** achieved TIR >80% and 56% achieved TIR =100% during their laboratory stay, compared to 38% and 6% under **SIT**, respectively. During this time, glycaemic variability was reduced by 6% with all patients achieving the target CV% of <36%[29] whilst concurrently avoiding increased exposure to hypoglycaemia. Further, this effect persisted over the course of the subsequent 48-hour free-living observation window with an improvement in daytime TIR of ~12%, with 66% of patients

under **SIT-LESS** achieving TIR >80% – double that achieved under **SIT**. Given that no differences were observed in dietary intake, insulin administration, or objectively assessed physical activity levels during this period, it is likely that persistence in glycaemic improvement under **SIT** is due to the residual effect from the interrupted sitting intervention rather than secondary to a change in behaviour. As such, our data demonstrate that the majority of patients adopting our strategy are able to achieve and exceed current mealtime glycaemic targets[29]. This a major finding given the inherent complexity and difficulty associated with optimising postprandial glucose management in T1D and that controlling postprandial glucose excursions is a key component of achieving recommended HbA1c levels and minimising disease burden. In reality, many patients are exposed to increased glycaemic variability and hypoglycaemia during mealtimes, both of which are significant sources of frustration for patients and factors that increase the risk of cardiovascular events and premature mortality independent of HbA1c[30].

A remarkable finding of the present study was that the magnitude of glycaemic improvement across our chosen CGM metrics (mean glucose, TIR, glycaemic variability) persisted beyond our controlled experimental observation window for up to a further 48-hours under free-living conditions. Importantly, time spent in nocturnal hyperglycaemia was on average 16% lower under **SIT-LESS** with minimal exposure to hypoglycaemia. Whereas our data highlight the detrimental and persistent effects of high levels of prolonged sitting in T1D, they also clearly demonstrate the glycaemic benefits of interrupting prolonged sitting and offer a strategy for incorporating more physical activity throughout the day whilst avoiding increased exposure to potentially dangerous hypoglycaemia. It remains unknown however, whether adopting a SIT-LESS protocol on consecutive days, or on multiple days per week results in further glucose lowering. Future work should assess the impact and safety of sustained adoption of SIT-LESS to establish whether combining activity days has continued or increased glucose lowering power.

Within our study, we also examined the potential impact of pre-treatment clinical characteristics on the magnitude of treatment response. Our data show that baseline HbA1c and BMI status are important clinical characteristics that strongly associate with the magnitude of glucose lowering, with patients presenting with poorer glucose control and increased BMI demonstrating, on average, the largest degree of glucose lowering. The measures employed within this study do not enable an exploration into the putative mechanisms underpinning the improvements in glycaemic control observed under **SIT-LESS**, nor the interaction between

HbA1c and BMI with treatment response. However, the standardisation of insulin administration and dietary intake across conditions, is suggestive of enhanced contraction-induced and/or energy deficit-induced insulin sensitivity[31], and/or a greater reliance on insulin-independent contraction-mediated glucose disposal[32]. As such, interrupting sitting may present an opportunity not only to tackle suboptimal glucose control, but also increase insulin sensitivity in those presenting with insulin resistance. Overweight, obesity, and insulin resistance have recently been shown to be highly prevalent within the T1D population and to be strongly associated with the risk of micro- and macrovascular complications independent of HbA1c[24]. Therefore, future studies are warranted that explore the longer-term impacts of interrupted sitting on insulin resistance in T1D. Furthermore, it would be beneficial to explore whether the additive effects of exercise and diet-induced energy deficit on glycaemic improvement extend to physical activities at the lowest-end of the physical activity continuum, in order to optimise lifestyle change prescription.

Strengths of this study include: the rigorous well-controlled randomised crossover study design allowing for within and between participant comparisons, increasing internal validity and reliability of the data collected, and permitting a smaller sample size whilst ensuring adequate statistical power. We standardised condition run-in periods with strict but pragmatic assessment and replication of confounding variables including diet, physical activity, fasting metabolic and glycaemic status, and experimental start time; comprehensive and blinded glucose profiling under controlled and extended free-living conditions with negligible data loss (<0.1%); full retention of study participants that reflect a relatively broad and representative demographic; and, the simple and practical nature of the intervention which enables widespread promotion and adoption. Key study limitations are that this is a single centre study with a conservative sample size which prevented subgroup analyses. Further, we assessed physical activity volume using total step count and were unable to assess other dimensions of physical activity and therefore cannot rule out the possibility that undetected changes in physical activity could have impacted glucose outcomes during the free-living period. Future research is needed to determine whether such an intervention can be optimised (frequency, intensity, and duration of walking breaks), and tailored specifically to accommodate patients with mobility issues, functional limitations, the presence of overt diabetes complications and other comorbidities, as well as those with insulin resistance. In addition, future studies should establish if such a strategy can be maintained by patients in free-living environments over the long-term and whether this translates to reduced risk of long-term complications and improved quality of life.

CONCLUSION

We show, for the first time, that interrupting prolonged sitting with frequent short bouts of light-intensity activity improves acute postprandial glucose control resulting in glucose lowering, improved TIR and reduced glycaemic variability without increased risk of hypoglycaemia, with sustained improvement for up to a further 48-hours. Although longer-term efficacy needs to be established, our findings provide the first experimental evidence for the value of frequent low intensity physical activity for improving glycaemia in individuals with T1D. This simple and acceptable approach may help to enable inactive individuals to incorporate more physical activity into the day and improve diabetes management. Interruption of sitting with light activities could be particularly useful for those who are unable or unwilling to engage in structured exercise, and this approach can be seen as an important "stepping-stone" toward regular participation in structured moderate-vigorous physical activity or exercise. It should be emphasised that, unlike moderate-vigorous exercise, the improvement in glycaemia with our simple intervention did not result in increased hypoglycaemia and therefore we propose that healthcare professionals consider advising patients to regularly interrupt prolonged sitting. Large scale studies are warranted to fully evaluate both the short- and long-term impact of this simple intervention in the management of individuals with T1D.

AUTHORSHIP

MDC: conceptualization, funding acquisition, investigation, methodology, resources, supervision, visualization, writing - original draft, writing – review and editing; AMA: investigation, visualization, writing - review and editing; MH: investigation, visualization, writing - review and editing; PCD: conceptualization, funding acquisition, investigation, methodology, resources, supervision, visualization, writing – review and editing; SMP: investigation, visualization, writing - review and editing; NK: investigation, visualization, writing - review and editing; RC: investigation, visualization, writing - review and editing; RAA: conceptualization, funding acquisition, investigation, methodology, resources, supervision, visualization, writing – review and editing. All authors had access to the data, approved the final version, and accept responsibility to submit for publication. This study was funded by Diabetes UK (20/0006154). The funder was not involved in the design of the study, data collection, analysis, or interpretation.

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CONFLICT OF INTEREST STATEMENT

No interests to declare.

DATA SHARING

Deidentified participant data collected during the trial alongside the study protocol and statistical analysis plan will be made available beginning 3 months and ending 36 months following article publication for investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals may be submitted up to 36 months following article publication and should be directed to matthew.campbell@sunderland.ac.uk to gain access, data requestors will need to sign a data access agreement. After 36 months the data will be available in our university's data warehouse but without investigator support other than deposited metadata.

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Table 1. CGM outcomes for the experimental and free-living phases in response to SIT versus SIT-LESS

	SIT	SIT-LESS	P Value
Pre-experimental phase (48-hour run-in period)			
Mean glucose (mmol/L)	7.7±1.1	7.5±2.1	0.631
Percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	79.1±12.5	81.1±19.9	0.561
Percent TAR >10.0 mmol/L (>180 mg/dL)	16.5±12.5	14.7±19.8	0.638
Percent TAR >13.9 mmol/L (>250 mg/dL)	2.7±4.1	4.9±13.1	0.293
Percent TBR <3.9 mmol/L (<70 mg/dL)	4.5±5.2	4.3±7.4	0.903
Percent TBR <3.0 mmol/L (<54 mg/dL)	0.6±1.4	4.0±7.0	0.326
Glycaemic variability (CV%)	31.4±10.6	28.7±9.7	0.104
Experimental phase response			
Mean glucose (mmol/L)	8.5±2.0	7.1±1.8	0.008**
Percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	70.9±27.4	88.0±19.9	0.007**
Percent TAR >10.0 mmol/L (>180 mg/dL)	26.5±27.5	8.6±18.3	0.004**
Percent TAR >13.9 mmol/L (>250 mg/dL)	6.9±14.3	1.7±6.5	0.072
Percent TBR <3.9 mmol/L (<70 mg/dL)	2.7±8.4	3.3±10.2	0.795
Percent TBR <3.0 mmol/L (<54 mg/dL)	0.7±3.7	0.2±1.2	0.536
Glycaemic variability (CV%)	24.4±13.0	18.1±9.2	0.013*
Free-living phase response			
Mean glucose (mmol/L)	8.1±1.3	6.9±1.5	<0.001***
Percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	71.6±19.3	84.6±14.8	0.004**
Percent TAR >10.0 mmol/L (>180 mg/dL)	23.8±18.6	9.6±11.6	<0.001***
Percent TAR >13.9 mmol/L (>250 mg/dL)	4.5±5.8	1.5±3.67	0.007**
Percent TBR <3.9 mmol/L (<70 mg/dL)	4.6±5.0	6.0±9.85	0.568
Percent TBR <3.0 mmol/L (<54 mg/dL)	1.3±2.3	1.8±4.5	0.529
Glycaemic variability (CV%)	31.7±12.4	24.5±11.9	0.035*
Combined free-living day time periods			

Mean glucose (mmol/L)	8.2±1.4	7.1±1.7	0.002**
Percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	71.0±18.6	82.5±19.0	0.023*
Percent TAR >10.0 mmol/L (>180 mg/dL)	24.3±18.8	11.0±15.7	0.003**
Percent TAR >13.9 mmol/L (>250 mg/dL)	19.6±16.1	9.0±12.1	0.017*
Percent TBR <3.9 mmol/L (<70 mg/dL)	4.7±6.1	11.0±10.9	0.478
Percent TBR <3.0 mmol/L (<54 mg/dL)	1.5±3.6	2.2±4.9	0.536
Glycaemic variability (CV%)	24.0±7.6	19.2±8.7	0.044*
Combined free-living night-time periods			
Mean glucose (mmol/L)	8.0±1.5	6.7±1.4	0.003**
Percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	71.6±23.3	86.6±14.3	0.003**
Percent TAR >10.0 mmol/L (>180 mg/dL)	22.9±22.2	7.2±11.1	0.001**
Percent TAR >13.9 mmol/L (>250 mg/dL)	3.5±6.3	0.5±1.6	0.007**
Percent TBR <3.9 mmol/L (<70 mg/dL)	5.4±7.2	6.8±11.0	0.606
Percent TBR <3.0 mmol/L (<54 mg/dL)	0.9±1.7	3.5±5.9	0.159
Glycaemic variability (CV%)	44.5±18.3	39.4±22.3	0.374

Note: Day time and nighttime periods calculated as the combined mean for each respective period. TIR = time in range; TAB = time above range; TBR = time below range; CV = coefficient of variation. *Indicates a conditional difference at P<0.05; **Indicates a statistically significant conditional difference at P<0.01; ***Indicates a statistically significant conditional difference at P<0.001. Data are presented as mean±SD.

Table 2. Association between pre-treatment clinical characteristics and treatment response

	HbA1c	BMI
Experimental and free-living phase response		
Mean change in mean glucose (mmol/L)	β = -0.801 (-1.39 to -0.78); P < 0.001***	β = -0.773 (-0.53 to -0.283); P =<0.001***
Mean change in percent TIR 3.9-10.0 mmol/L (70-180 mg/dL)	β = 0.462 (2.18 to 13.14); P = 0.008**	β = 0.481 (0.97 to 5.22); P = 0.005**
Mean change in percent TAB >10.0 mmol/L (>180 mg/dL)	β = -0.686 (-14.72 to -6.37); P < 0.001***	β = -0.740 (-5.94 to -2.93); P < 0.001***
Mean change in percent TBR <3.9 mmol/L (<70 mg/dL)	β = 0.343 (-0.064 to -5.84); P = 0.049*	β =- 0.404 (-0.208 to -2.45); P = 0.022*
Mean change in glycaemic variability (CV%)	β = 0.052 (-4.241 to 5.624); P = 0.777	β = 0.108 (-1.36 to 2.47); P =0.558

Note: Data presented as unstandardized β-coefficients (95% confidence interval); BMI = body mass index; *Indicates a statistically significant association at P<0.05; **Indicates a statistically significant association at P<0.01; ***Indicates a statistically significant association at P<0.001.

FIGURE LEGENDS

Figure 1. Glycaemic responses to interrupting sitting with frequent short bouts of light-intensity activity. Grey trace = **SIT** (uninterrupted sitting); Black trace = **SIT-LESS** (interrupted sitting with 3-minute bouts of self-paced light-intensity walking at 30-minute intervals as indicated by black vertical arrows). *Indicates a statistically significant conditional difference during each respective time-period at P<0.05. **Indicates a statistically significant conditional difference during each respective time-period at P<0.01; ***Indicates a statistically significant conditional difference during each respective time-period at P<0.001; Vertical dashed line breaks indicate nocturnal periods. Data presented as mean (solid trace) with SD (dashed trace); To improve clarity, +SD is presented for SIT, and -SD is presented for SIT-LESS.

Figure 2. Individualized magnitude of change in treatment response between **SIT** and **SIT-LESS** across: A: mean glucose, B: mean TIR, C: mean TAR, D: mean TBR, E: mean GV. Circles = pre-treatment HbA1c ≥7.5 mmol/mol; Triangles = pre-treatment HbA1c <7.5 mmol/mol. White data points = normal weight (<25 kg/m^2); Grey data points = overweight (25-29.9 kg/m^2); Black data points = obese (>29.9 kg/m^2). Numbers represent individually annotated participant data points. Treatment response calculated by subtracting mean **SIT-LESS** responses from mean **SIT** responses. **SIT** = uninterrupted sitting; **SIT-LESS** = interrupted sitting with 3-minute bouts of self-paced light-intensity walking at 30-minute intervals. TIR = time in range (3.9 – 10.0 mmol/L), TAR = time above range (>10 mmol/L), TBR = time below range (<3.9 mmol/L), GV = glycaemic variability (CV%). *Indicates a statistically significant association with magnitude of treatment response at P<0.05. **Indicates a statistically significant association with magnitude of treatment response at P<0.01; ***Indicates a statistically significant association with magnitude of treatment response at P<0.

FIGRURES

Figure 1.

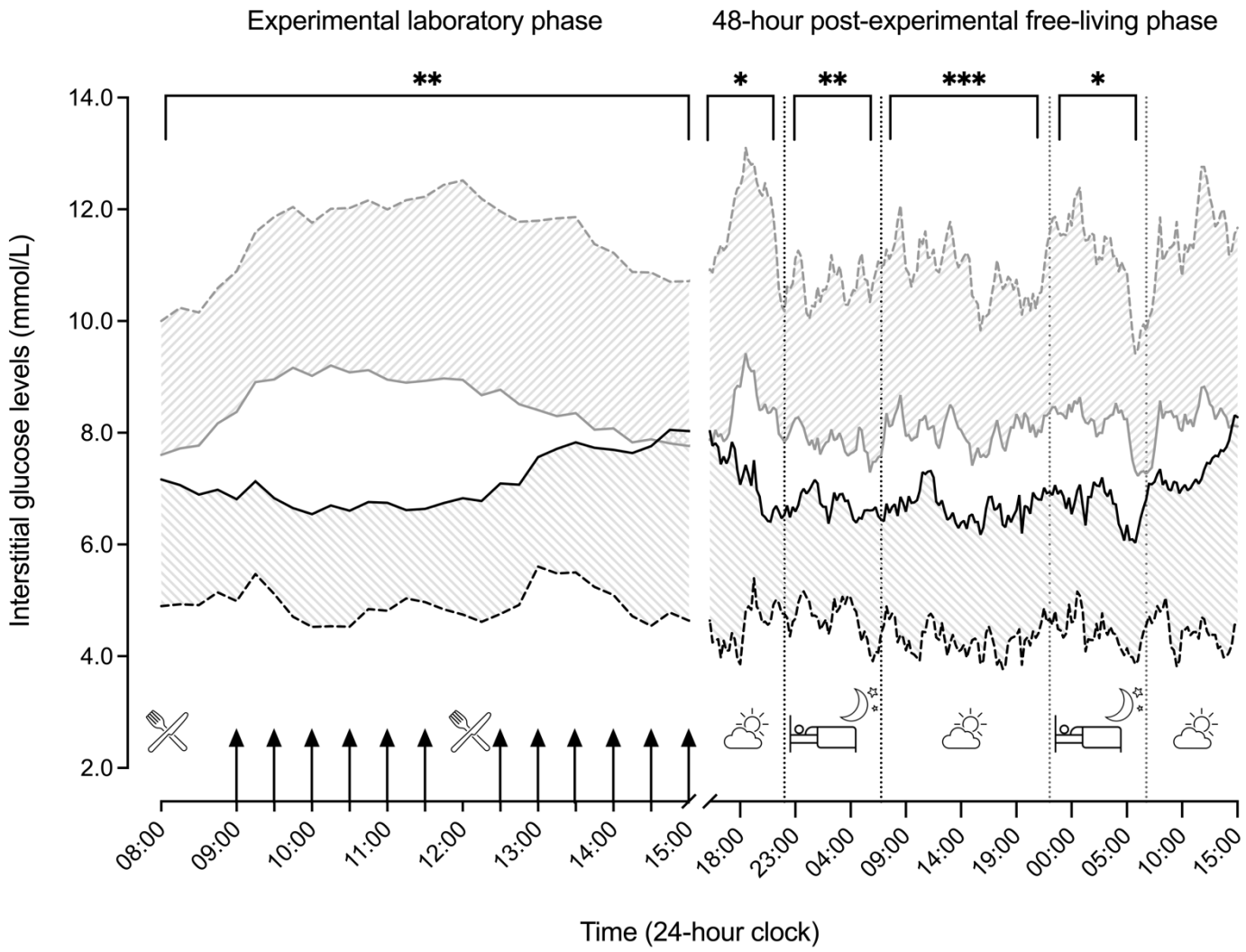
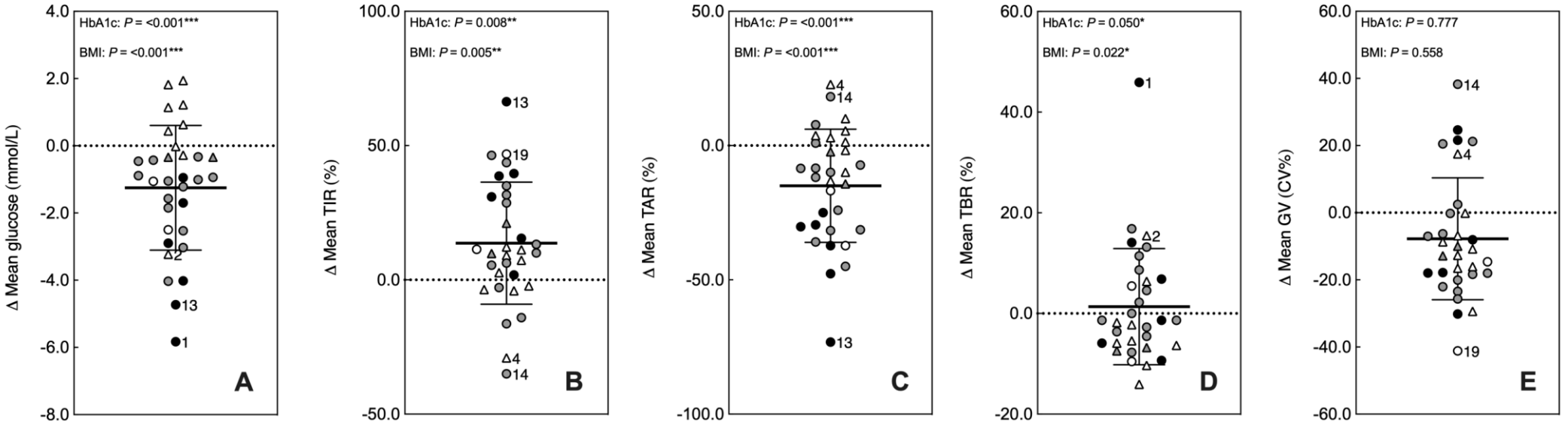


Figure 2.


HbA1c: P = <0.001***
BMI: P = <0.001***
Δ Mean glucose (mmol/L)
A
HbA1c: P = 0.008**
BMI: P = 0.005**
Δ Mean TIR (%)
B
HbA1c: P = <0.001***
BMI: P = <0.001***
Δ Mean TAR (%)
C
HbA1c: P = 0.050*
BMI: P = 0.022*
Δ Mean TBR (%)
D
HbA1c: P = 0.777
BMI: P = 0.558
Δ Mean GV (CV%)
E