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Human Kinetics
ORIGINAL RESEARCH

Acute Effects of Frequent Light-Intensity Standing-Based Exercises That Interrupt 8 Hours of Prolonged Sitting on Postprandial Glucose in Stroke Survivors: A Dose-Escalation Trial

Paul Mackie, Gary Crowfoot, Prajwal Gyawali, Heidi Janssen, Elizabeth Holliday, David Dunstan, and Coralie English

Background: Interrupting prolonged sitting can attenuate postprandial glucose responses in overweight adults. The dose–response effect in stroke survivors is unknown. The authors investigated the effects of interrupting 8 hours of prolonged sitting with increasingly frequent bouts of light-intensity standing-based exercises on the postprandial glucose response in stroke survivors. **Methods**: Within-participant, laboratory-based, dose-escalation trial. Participants completed three 8-hour conditions: prolonged sitting and 2 experimental conditions. Experimental conditions involved light-intensity standing-based exercises of increasing frequency (2×5 min to 6×5 min bouts). Postprandial glucose is reported. **Results**: Twenty-nine stroke survivors (aged 66 y) participated. Interrupting 8 hours of prolonged sitting with light-intensity standing-based exercises every 90 minutes significantly decreased postprandial glucose (positive incremental area under the curve; −1.1 mmol/L·7 h; 95% confidence interval, −2.0 to −0.1). In the morning (08:00–11:00), postprandial glucose decreased during the 4×5 minutes and 6×5 minutes conditions (positive incremental area under the curve; −0.8 mmol/L·3 h; 95% confidence interval, −1.3 to −0.3 and −0.8 mmol/L·3 h; 95% confidence interval, −1.5 to −0.2, respectively) compared with prolonged sitting. **Conclusion**: Interrupting 8 hours of prolonged sitting at least every 90 minutes with light-intensity standing-based exercises attenuates postprandial glucose in stroke survivors. During the morning, postprandial glucose is attenuated when sitting is interrupted every 60 and 90 minutes.

Keywords: clinical research, exercise, metabolic health

Time spent in prolonged sitting is associated with detrimental impacts on cardiometabolic health, notably through alterations in lipid and glucose metabolism (dysglycemia).[1–3] Dysglycemia is strongly associated with an increased risk of developing diabetes.[4] Diabetes leads to an increased risk of mortality, reduced functional outcome, and increased risk of recurrent stroke in stroke survivors.[5–7] With a high prevalence of stroke survivors living with prediabetes (approximately 23%–53%)[8,9] or diabetes (approximately 16%–43%),[5,9,10] improved glucose regulation is fundamental in the management of post stroke outcomes.

Regular engagement in physical activity is beneficial for managing dysglycemia and diabetes.[11,12] Despite this, many stroke survivors retain sedentary lifestyles,[13–15] spending up to 75% of their waking day sitting[13,14] and this frequently coincides with low levels of physical activity (light intensity; 23%, moderate- to vigorous-intensity physical activity; 0.5%).[14] Promisingly, evidence suggests that interrupting prolonged sitting with brief bouts of physical activity or standing may attenuate postprandial glucose responses.[2,16,17] Dempsey et al[18] found that among participants with type 2 diabetes, postprandial glucose was decreased by an average of 39% when 8 hours of prolonged sitting was interrupted with frequent short bouts (3 min every 30 min) of resistance activities while standing (knee raises, calf raises, gluteal contractions, and mini squats). However, these findings are in contrast with that of an experimental trial completed in stroke survivors (BUST-Stroke).[19] In the BUST-Stroke trial, postprandial glucose was not attenuated when 8 hours of prolonged sitting was interrupted with 3-minute bouts of light-intensity standing exercises (calf raises, mini squats, and marching on the spot) or walking (every 30 min).[19] These findings on the acute postprandial response in stroke survivors are unexpected, particularly since the BUST-Stroke trial reported significant benefits on other outcomes of cardiometabolic health (systolic blood pressure).[20] Therefore, further investigation is warranted to characterize the effects of different doses of light-intensity standing exercises on the acute postprandial glucose response in stroke survivors.

We investigated the effects of interrupting 8 hours of prolonged sitting with different doses of light-intensity exercises while

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standing (STAND-EX) in stroke survivors. Specifically, the study aimed to examine the effect of increasing the frequency of light-intensity standing-based exercises on the postprandial glucose response.

Methods

Design

This manuscript reports results for the predetermined secondary outcome (postprandial plasma glucose) from a laboratory-based, dose-escalation trial, the methods of which have been previously described.[21] Briefly, stroke survivors recruited from the Newcastle and Hunter region (NSW, Australia) attended the Hunter Medical Research Institute on 4 separate occasions (Figure 1). Participants undertook a familiarization session and three 8-hour conditions in cohorts of 10 participants. Conditions included a control condition (prolonged sitting) and 2 experimental conditions (sitting interrupted with light-intensity exercises [described below] while standing [STAND-EX]). Conditions increased in the frequency of STAND-EX bouts until a dose-limiting threshold was attained; inability of participants to achieve 80% of the target duration in STAND-EX and ≥70% of the cohort achieving the dose-limiting threshold. In brief and as detailed in Table 1, cohort 1 completed experimental condition 1 (2 × 5 min STAND-EX bouts) and experimental condition 2 (4 × 5 min STAND-EX bouts). Cohort 2 completed experimental condition 2 (4 × 5 min STAND-EX bouts) and experimental condition 3 (6 × 5 min STAND-EX bouts). At the dose-limiting threshold, we planned for a final cohort to complete the second to last cohort to confirm the optimal dose of STAND-EX. This trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001517369) and approved by the University of Newcastle's Human Research Committee (H-2017-0296) and Hunter New England Research Ethics Committee (17/06/21/4.04). Prior to commencement, written and verbal informed consent was provided by all participants.

Participants

Adult stroke survivors (≥18 y; >3 mo post stroke) were included if they: self-reported sitting for ≥7 hours per day; and could walk at ≥0.4 m/s with minimal assist (functional ambulation classification ≥3). They were excluded if they: had a body mass index >45 kg/m^2, had urinary frequency, self-reported moderate to vigorous physical activity ≥150 minutes per week, took diabetes medication (other than metformin), were diagnosed with diabetes, were a smoker, or were pregnant.

The initial familiarization visit included collection of the following baseline characteristics: stroke profile (National Institute of Health Stroke Scale,[22] Oxfordshire classification)[23]; walking speed (10-m walk test); type 2 diabetes mellitus risk (Australian type 2 diabetes risk assessment tool)[24]; fatigue (Fatigue Assessment Scale)[25]; medications; and habitual dietary intake (24 h recall). Physical activity (walking and standing) and sitting (sitting/lying) time were measured using the activPAL3 monitor (activPAL3; PAL Technologies Ltd, Glasgow, Scotland), positioned on the thigh of the nonparetic limb. The activPAL3 monitor recorded physical activity and sitting time for a minimum of 3 days prior to, during, and post experimental conditions. ProcessingPAL software (version 1.3; Leicester, United Kingdom), using validated algorithms, determined valid monitor wear time during waking hours. A day was deemed valid if (1) time spent in one activity was <95% of a day and (2) monitor wear time was >10 hours per day,[26] and participants took >100 steps.

Experimental Conditions

In each cohort, participants completed an 8-hour control condition (prolonged uninterrupted sitting) and 2 experimental conditions (Tables 1 and 2), separated by a minimum 4-day washout period. Participants were provided with an individualized meal plan and a standardized evening meal 24 hours prior to commencing each condition. Individual energy requirements for prescribed meals were estimated from the Schofield equation[27] for calculating basal metabolic rate, using weight, age, and appropriate physical activity levels (1.3 = sedentary adults). Participants were instructed 48 hours prior to conditions to abstain from exercise (moderate- to vigorous-intensity physical activity), caffeine, and alcohol.

On arrival following a 12-hour overnight fast, an intravenous cannula was inserted into the upper limb and fasting blood samples were collected at 08:00 and 08:30. Participants consumed a standardized breakfast from 08:30 to 09:00. The trial began at 09:00 and ceased at 16:00. Under supervised conditions, participants raised from a seated position only to complete the prescribed 5-minute doses of STAND-EX (Table 2), or to void. Each STAND-EX bout consisted of calf raises, mini squats, and marching on the spot (20 s on each exercise, repeated 5 times) completed at a Borg rating of perceived exertion of ≤3 (light intensity).[28] At 12:30 to 13:00, participants consumed a standardized lunch. Water intake (ad libitum) was recorded during the control condition and kept consistent throughout conditions.

Breakfast comprised of white bread (toasted) with a choice of butter, honey, or jam, prepacked cereal (Special K or corn flakes) with semiskimmed milk, apple, or orange juice and decaffeinated coffee or tea. Lunch comprised a frozen prepackaged meal (lean cuisine), a choice of apple or orange juice and a fruit cup (2 fruits or peach). Standardized meals were modified accordingly to contain approximately one-third of participants' estimated daily energy requirements, with a combined macronutrient content of 61% carbohydrate, 20% fat, and 16% protein.

Outcome Measures and Blood Analysis

The predetermined secondary outcome was within-participant, between-condition differences in postprandial plasma glucose response. Postprandial glucose is reported as the positive incremental area under the curve (+iAUC) calculated using the trapezoidal method. The +iAUC describes the positive area under the curve above the baseline value (08:00 AM fasting blood sample).[29] Any value below baseline was treated as the 08:00 AM baseline value. Blood samples were collected in a 4-mL ethylenediaminetetraacetic acid tube every 30 minutes during each 2-hour postprandial period (Table 3), prior to scheduled bouts of STAND-EX. Blood samples were refrigerated immediately and were centrifuged (15 min at −2000*g*) on average within 18 (0.01) minutes from collection. Plasma aliquots were stored at −80°C for later analyses. All plasma glucose was analyzed in duplicate using the Abbott Point of Care blood analysis device (i-STAT; Abbott Point of Care Inc, Sydney, Australia).

Data Analysis

A statistical analysis plan was outlined a priori[21] to detect within-person, between-condition differences in the primary outcome systolic blood pressure. The secondary outcome postprandial

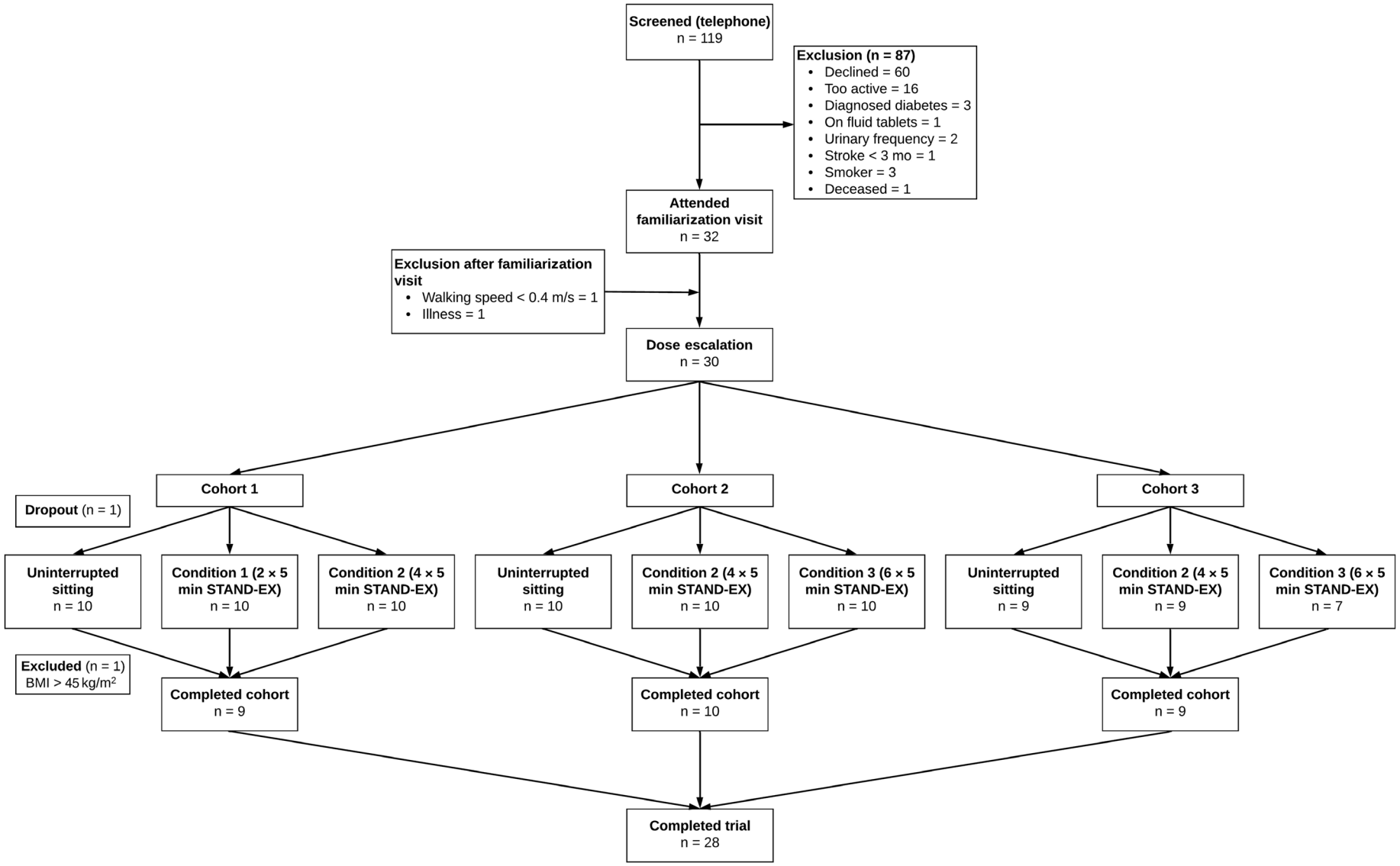

Figure 1 — Flow of participants. BMI indicates body mass index; STAND-EX, light-intensity exercises while standing.

Table 1 Experimental Conditions by Cohort

	Sitting (8 h)	Condition 1 (2 × 5 min)	Condition 2 (4 × 5 min)	Condition 3 (6 × 5 min)	Condition 4 (8 × 5 min)	Condition 5 (10 × 5 min)
Cohort 1						
Cohort 2						
Cohort 3						
Cohort 4						
Cohort 5						

glucose is reported as the positive incremental area under the curve (+iAUC). Simple imputation methods were used to impute a small proportion of missing values. Each missing value was imputed as a simple average of 2 values: (1) the mean of the 2 observed values at immediately adjacent timepoints *within* the participant, and (2) the mean observed value at the missing timepoint *between* participants. When a participant also had a missing value at either adjacent timepoint, the missing value was imputed simply as the value from (2).

Linear mixed models were used to estimate between-condition differences in glucose +iAUC, controlling for condition and time (fixed effects), and repeated measures on participants (using a random intercept). The initial morning meal has been suggested to contribute to daily variations in glycemic control.[30] Fletcher et al[30] reported in adolescents a significantly greater glucose incremental area under the curve (iAUC) following the breakfast only. In stroke survivors[19] and those with type 2 diabetes,[18] glucose concentrations were also demonstrated to be greater following the morning breakfast meal. Therefore, exploratory analysis examined between-condition effects in glucose +iAUC during the 3-hour morning period (08:00–11:00). Statistical significance was set at 5% ($P < .05$) for all analyses. Data are represented as mean (SD) unless otherwise stated.

Results

Participants

Thirty-two participants were recruited and completed the familiarization session (Figure 1). Three withdrew and one was excluded due to not meeting the inclusion criteria (body mass index >45 kg/m^2). Overall, 28 participants were included in the final analysis and 26 completed all experimental conditions (Figure 1). Due to the COVID-19 pandemic (2020), 2 participants were unable to complete their final visit (6 × 5 min condition) and the final participant could not be recruited. Three experimental conditions were tested (2 × 5 min, 4 × 5 min, and 6 × 5 min).

Table 3 details participant characteristics. Participants were on average 74 (90) months post stroke, with a mean age of 67 (13) years, and were classified as having a minor stroke (National Institute of Health Stroke Scale score 1–4). Participants spent on average 10.4 (2.9) hours per day sitting, 3.5 (1.7) hours per day standing, and 1.2 (0.6) hours per day walking over the (minimum) 4 days prior to completing their first experimental condition. On the days after the experimental conditions, participants spent slightly more time standing and walking, but the magnitude of this difference is not clinically important. For example, participants took on average 348 more steps (95% confidence interval [CI], 20 to 676) in the days following the 2 × 5 minutes condition, compared with the 4 days prior to their first experimental condition. Participants also spent 0.5 hours per day more in standing (95% CI, 0.1 to 0.9) in the days following the 6 × 5 minutes condition compared with the 4 days prior to completing their first experimental condition.

Effects of STAND-EX on Postprandial Glucose

Table 4 details between-condition differences in glucose +iAUC during the 8-hour experimental conditions and the 3-hour morning period. Overall, 133 (12%) data points were missing across all participants.

Glucose +iAUC was significantly decreased during the 4 × 5 minutes condition compared with prolonged sitting (−1.1 mmol/L·7 h; 95% CI, −2.0 to −0.1) (Figure 2). Glucose +iAUC did not differ significantly in the 2 × 5 minutes condition or the 6 × 5 minutes condition, compared with prolonged sitting. During the 3-hour morning period, glucose +iAUC was significantly lower during both the 4 × 5 minutes condition (−0.8 mmol/L·3 h; 95% CI, −1.3 to −0.3) and 6 × 5 minutes condition (−0.8 mmol/L·3 h; 95% CI, −1.5 to −0.2) compared with prolonged sitting (Figure 2). The glucose +iAUC did not significantly differ in the 2 × 5 minutes condition compared with prolonged sitting.

Discussion

In stroke survivors, interrupting 8 hours of prolonged sitting during the 4 × 5 minutes condition (equating to one bout every 90 min) with light-intensity standing-based exercises decreased the postprandial glucose response (15% reduction) over 8 hours. A decrease in postprandial glucose was also found during the morning period (08:00–11:00) of the 4 × 5 minutes (21% reduction) and 6 × 5 minutes (17% reduction) conditions, when compared with prolonged sitting.

This trial builds on the evidence that has shown that frequently interrupting prolonged sitting time with bouts of physical activity or standing improves measures of cardiometabolic health[16,31] and adds new insights into the morning postprandial glucose responses in stroke survivors. Elevations in 2-hour postprandial glucose are associated with an increased risk of mortality, cardiovascular disease,[32,33] ischemic stroke, and coronary heart disease.[34] Repeated glucose elevations have been shown to be associated with an increased risk of diabetes-related and cardiovascular complications, inducing an increase in oxidative stress, resulting in endothelial dysfunction.[33,35] Our findings are consistent with other

Table 2 Schedule of Experimental Conditions and Measurements

Conditions and measurements	Time, h																
	08:00	08:30	09:00	09:30	10:00	10:30	11:00	11:30	12:00	12:30	13:00	13:30	14:00	14:30	15:00	15:30	16:00
Exp condition 1		→		→	→	→	→	→	→	→		→	→	→	→	→	→
Exp condition 2		→		→	→	→		→	→	→		→	→	→		→	→
Exp condition 3		→		→		→		→	→	→		→		→		→	→
Exp condition 4		→				→		→	→	→				→		→	→
Exp condition 5		→						→	→	→						→	→
Standard meal		Meal								Meal							
Blood pressure	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP	BP
Blood collection	Bld	Bld	Bld	Bld	Bld	Bld	Bld			Bld	Bld	Bld	Bld	Bld	Bld		
Fatigue	FVAS				FVAS				FVAS						FVAS		FVAS

Abbreviations: →, prolonged sitting bout; Bld, blood; BP, blood pressure; Exp, experimental; FVAS, visual analog scale for fatigue.

Table 3 Characteristics of Participants

Characteristics	Cohort 1 (n = 9)	Cohort 2 (n = 10)	Cohort 3 (n = 9)	Total (N = 28)
Age, y (mean [SD])	66 (15)	67 (8)	67 (16)	67 (13)
Sex, number male (%)	5 (56)	4 (40)	6 (67)	15 (54)
Weight, kg (mean [SD])	87.4 (12.0)	81.8 (16.9)	89.9 (23.3)	86 (18)
Height, m (mean [SD])	1.67 (0.11)	1.65 (0.08)	1.73 (0.08)	1.68 (0.09)
BMI, kg/m^2 (mean [SD])	31.3 (2.7)	30.2 (6.1)	29.9 (5.9)	30.4 (5.0)
Waist circumference, cm (mean [SD])	102 (12)	100 (14)	105 (17)	103 (14)
Time since stroke, mo (mean [SD])	96 (105)	46 (52)	81 (108)	74 (90)
AUSDRISK, mean (SD)	14 (5)	17 (4)	17 (5)	16 (5)
Medications, number yes (%)				
Anticoagulants	7 (78)	8 (80)	4 (44)	19 (68)
Antidepressants	2 (22)	2 (20)	0 (0)	4 (14)
Cholesterol lowering	4 (44)	7 (70)	5 (56)	16 (57)
Antihypertensive	4 (44)	6 (60)	6 (67)	16 (57)
Walking aid, number yes (%)	7 (78)	8 (80)	5 (56)	7 (25)
Walking speed, m/s (mean [SD])	1.1 (0.3)	1.2 (0.2)	0.8 (0.3)	1.0 (0.3)
National Institute of Health Stroke Scale, mean (SD)	3.0 (3.9)	2.3 (2.2)	4.6 (4.9)	3.2 (3.7)
No symptoms (score 0), number yes (%)	2 (22)	2 (20)	0 (0)	4 (15)
Mild (score 1–4), number yes (%)	5 (56)	6 (60)	5 (63)	16 (60)
Moderate (score 5–15), number yes (%)	2 (22)	2 (20)	3 (38)	7 (27)
Oxfordshire classification categories, number (%)				
TACI	0 (0)	1 (11)	1 (11)	2 (7)
PACI	3 (33)	4 (44)	4 (44)	11 (41)
Lacunar	2 (22)	0 (0)	0 (0)	2 (7)
POCI	1 (11)	0 (0)	0 (0)	1 (4)
Hemorrhage	3 (33)	4 (44)	4 (44)	11 (41)
Side of hemiparesis, number left (%)	5 (56)	6 (60)	4 (44)	15 (54)
No hemiparesis, number yes (%)	0 (0)	1 (10)	0 (0)	1 (4)

Abbreviations: BMI, body mass index; AUSDRISK, Australian type 2 diabetes risk; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct.

Table 4 Mean (SD) of Conditions for Glucose and +iAUC Across a Day and During the Morning, and Estimated Mean (95% CI) Difference Between Conditions

	Conditions				Difference between conditions		
Outcome	Sitting, n = 28	2 × 5 min condition, n = 9	4 × 5 min condition, n = 28	6 × 5 min condition, n = 17	2 × 5 min condition minus sitting	4 × 5 min condition minus sitting	6 × 5 min condition minus sitting
Fasting glucose, mmol/L	5.8 (0.9)	5.4 (0.3)	5.8 (1.1)	6.0 (1.2)	0.05 (–0.21 to 0.31)	0.1 (–0.1 to 0.3)	–0.02 (–0.22 to 0.17)
Average glucose across day, mmol/L	6.9 (1.8)	6.4 (1.2)	6.7 (1.7)	6.9 (1.8)	–0.1 (–0.4 to 0.2)	–0.1 (–0.3 to 0.1)	–0.2 (–0.4 to 0.1)
Glucose +iAUC, mmol/L·7 h	8.6 (4.3)	7.1 (2.9)	7.3 (4.5)	7.7 (4.4)	–0.4 (–2.0 to 1.1)	–1.1 (–2.0 to –0.1)	–0.9 (–2.1 to 0.3)
Glucose +iAUC morning, mmol/L·3 h	4.8 (2.3)	3.5 (1.4)	3.8 (2.2)	4.0 (2.5)	–0.5 (–1.3 to 0.4)	–0.8 (–1.3 to –0.3)	–0.8 (–1.5 to –0.1)
Degree of difficulty, RPE 0–10; 0 = not difficult	0.9 (1.8)	0.7 (1.3)	0.8 (1.5)	0.2 (0.6)	–0.4 (–1.1 to 0.4)	–0.2 (–0.7 to 0.3)	–0.4 (–1.0 to 0.2)
Fatigue, VAS 0–10; 0 = not fatigued	2.1 (2.1)	2.1 (2.4)	1.7 (2.3)	1.0 (1.5)	–0.6 (–1.2 to –0.1)	–0.4 (–0.7 to –0.1)	–0.7 (–1.1 to –0.3)

Abbreviations: +iAUC, positive incremental area under the curve; CI, confidence interval; RPE, ratings of perceived exertion; VAS, visual analog scale.

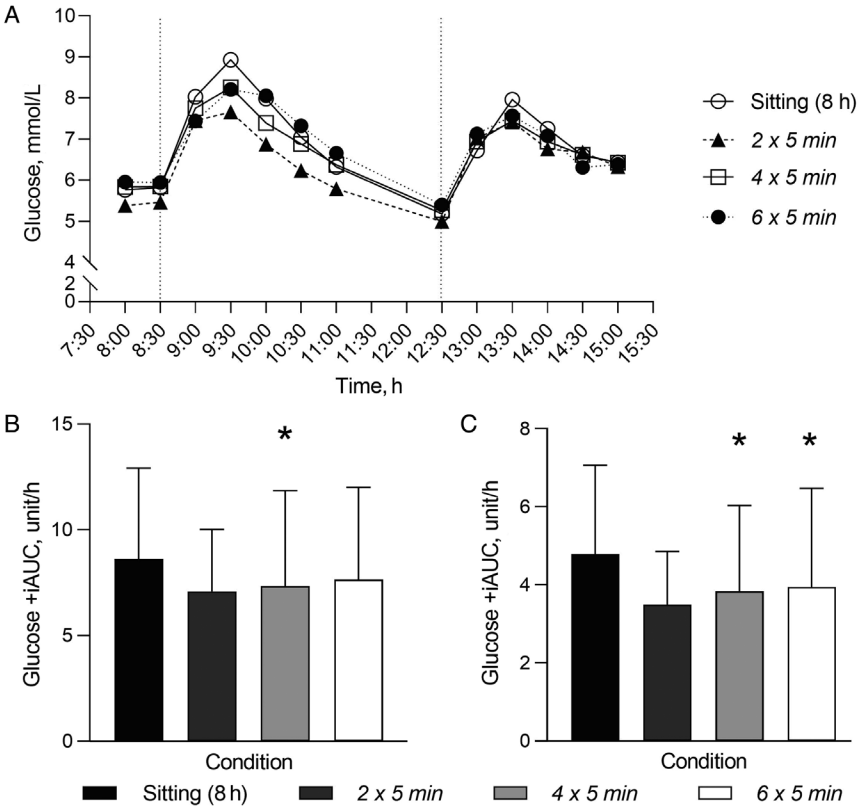

Figure 2 — (A) Mean glucose responses across a day during each condition. (B) and (C) Mean (SD) glucose +iAUC across a day and during the morning period (08:00–11:00), respectively. Vertical dashed lines in (A) indicate breakfast (08:30) and lunch (12:30) meals. +iAUC indicates positive incremental area under the curve. $^{*}P < .05$.

clinical populations that report an acute decrease in postprandial glucose of between 24% and 39% in response to frequent short bouts of activity in those who are healthy, overweight or obese, or have type 2 diabetes.[18,36,37] However, bouts of walking and simple resistance activities in these studies were more frequent (every 20–30 min) compared with the current trial (every 60–90 min). Taking into consideration that many stroke survivors are unable to meet the minimum recommended physical activity guidelines,[38–40] our findings suggest that interrupting prolonged sitting every 60 to 90 minutes might be a feasible approach in stroke survivors with mild walking disability. Furthermore, interrupting prolonged sitting with frequent bouts of standing-based exercises might be an important strategy in controlling postprandial glucose regulation and consequently, could help to reduce the risk of developing cardiovascular and diabetes complications.

In contrast to our results, the only previous trial conducted in stroke survivors (BUST-Stroke trial)[19] reported no significant differences in postprandial glucose when 8 hours of prolonged sitting was interrupted (every 30 min) with 3-minute bouts of STAND-EX or walking.[19] The characteristics of included participants in BUST-Stroke were similar to our trial (mean age, 68 and 67 y; National Institute of Health Stroke Scale, 3.6 and 3.2; Australian type 2 diabetes risk, 16 and 16; body mass index 29.9 and 30.4, respectively). The discrepancy in results between BUST-Stroke and our study may be due to differences in methodology. In the BUST-Stroke trial,[19] blood samples were processed within 1 to 2 hours after collection in comparison with the average processing time in our trial of 18 (0.01) minutes. Delays of up to 2 hours in blood processing can lead to reductions of 46% in plasma glucose concentrations, compared within baseline concentrations.[41] Thus, the longer and more varied time between blood collection and blood processing in the BUST-Stroke trial might partly explain the variations in postprandial glucose response. In addition, the high intraassay coefficient of variants reported in the BUST-Stroke trial (<15%) might have also influenced results. Therefore, well-controlled blood processing designs are essential in future trials to confirm the effects of interrupting prolonged sitting time on postprandial glucose response in stroke survivors.

The primary strength of this trial was the timely processing of blood samples, and control of confounding variables. Although blood analysis was not blinded, blood samples were analyzed using the Abbott point of care analysis system (I-STAT) in duplicate. However, the following limitations must be considered. This trial was powered to detect within-person, between-condition differences in the primary outcome (systolic blood pressure). Therefore, we may have been underpowered to detect significant differences at the lower doses for postprandial glucose. In addition, exploratory analysis during the 3-hour morning period were based upon assumptions from previous trials[18,19,30] and limits conclusions on experimental condition effects. Finally, no multiple adjustment testing was performed due to the small sample size of cohorts, increasing the risk of type I errors.

Engaging in light-intensity standing-based exercises every 90 minutes was observed to attenuate postprandial glucose during the morning, and over an 8-hour day in stroke survivors. More frequent (every 60 min) bouts of standing-based exercises also attenuated postprandial glucose during the morning period. However, the magnitude of reduction did not differ between the

4 × 5 minutes and 6 × 5 minutes conditions during the morning period. These findings suggest the importance of frequently interrupting prolonged sitting for postprandial glucose control in stroke survivors. However, the effect of interrupting prolonged sitting time in glucose regulation in real-world settings and over longer periods, still needs to be assessed.

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