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Short, frequent, light-intensity walking activity improves postprandial vascular-inflammatory biomarkers in people with type 1 diabetes: The SIT-LESS randomized controlled trial

Nawaz Z. Safdar MBChB^{1,2}  | Anwar M. Alobaid MSc^{3,4} | Mark Hopkins PhD³ |
 Paddy C. Dempsey PhD^{5,6,7,8} | Sam M. Pearson MBBS¹  |
 Noppadol Kietsiroje^{1,9}  | Rachel Churm PhD¹⁰ | Ramzi A. Ajjan MD¹ |
 Matthew D. Campbell PhD^{1,5,11} 

¹Leeds Institute of Cardiovascular and Metabolic Medicine, Faculty of Medicine, University of Leeds, Leeds, UK

²Department of Internal Medicine, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK

³School of Food Science and Nutrition, Faculty of Environment, University of Leeds, Leeds, UK

⁴Ministry of Health, Farwaniya Hospital, Kuwait City, Kuwait

⁵Institute of Metabolic Science, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

⁶Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

⁷Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

⁸Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia

⁹Endocrinology and Metabolism Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

¹⁰Applied Sports Technology, Exercise and Medicine (A-STEM) Research Centre, Faculty of Science and Engineering, Swansea University, Swansea, UK

¹¹John Dawson Drug Discovery and Development Institute, University of Sunderland, Sunderland, UK

Correspondence

Dr Matthew D. Campbell, John Dawson Drug Discovery and Development Institute, Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland UK.

Email: matthew.campbell@sunderland.ac.uk

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Abstract

Aim: To examine the effect of interrupting prolonged sitting with short, frequent, light-intensity activity on postprandial cardiovascular markers in people with type 1 diabetes (T1D).

Materials and Methods: In a randomized crossover trial, 32 adults with T1D (mean \pm SD age 28 ± 5 years, glycated haemoglobin 67.9 ± 12.6 mmol/mol, 17 women) completed two 7-h laboratory visits separated by >7 days. Participants either remained seated for 7 h (SIT) or interrupted sitting with 3-min bouts of self-paced walking at 30-min intervals commencing 1 h after each meal (SIT-LESS). Physical activity, insulin regimen, experimental start times, and meal consumption were standardized during each arm. Plasma levels of interleukin (IL)-1 β , tumour necrosis factor (TNF)- α , plasminogen activator inhibitor (PAI)-1 and fibrinogen were sampled at baseline, 3.5 and 7 h, and assessed for within- and between-group effects using a repeated measures ANOVA. The estimated glucose disposal rate was used to determine the insulin resistance status.

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Results: Vascular-inflammatory parameters were comparable between SIT and SIT-LESS at baseline ($p > .05$). TNF- α , IL-1 β , PAI-1 and fibrinogen increased over time under SIT, whereas these rises were attenuated under SIT-LESS ($p < .001$). Specifically, over the 7 h under SIT, postprandial increases were detected in TNF- α , IL-1 β , PAI-1 and fibrinogen (+67%, +49%, +49% and +62%, respectively; $p < .001$ for all). Conversely, the SIT-LESS group showed no change in IL-1 β (−9%; $p > .50$), whereas reductions were observed in TNF- α , PAI-1 and fibrinogen (−22%, −42% and −44%, respectively; $p < .001$ for all). The intervention showed enhanced effects in insulin-resistant individuals with T1D.

Conclusions: Interrupting prolonged sitting with light-intensity activity ameliorates postprandial increases in vascular-inflammatory markers in T1D.

Trial Registration: The trial was prospectively registered (ISRCTN13641847).

KEYWORDS

inflammation, physical activity, sedentariness, thrombosis, type 1 diabetes

1 | INTRODUCTION

Sedentary behaviours, including prolonged periods of uninterrupted sitting, are prevalent in type 1 diabetes (T1D)¹ and increase cardiovascular risk.^{2,3} A number of inflammatory and thrombotic molecules have been implicated in cardiovascular pathology, including tumour necrosis factor (TNF)- α , interleukin (IL)-1 β , plasminogen activator inhibitor (PAI)-1 and fibrinogen.⁴ Data from previous studies indicate that sitting for prolonged periods predisposes to an adverse cardiovascular inflammatory/metabolic environment,⁵ including poorer glucose control,⁶ insulin resistance⁷ and an increased vascular-inflammatory milieu.^{8,9} We have previously shown vascular-inflammatory and thrombotic markers to be raised in people with T1D, particularly those presenting with concomitant insulin resistance.^{10–12} However, it is unclear whether reversing the sedentary behaviour modulates the thrombo-inflammatory milieu in individuals with T1D.

Studies in individuals with type 2 diabetes (T2D) and those with normoglycaemia have shown that reducing and breaking up prolonged periods of sitting with brief bouts of light-intensity activity improves vascular-inflammatory risk factors in people with and without T2D.^{13,14} However, these data remain preliminary and limited to individuals with, or at risk of, developing T2D. Recently, we showed that interrupting prolonged sitting with short, frequent, light-intensity activity improves glucose control in people with T1D.¹⁵ Furthermore, the magnitude of improvement was greatest in those with higher pre-treatment glycated haemoglobin (HbA1c), body mass index and insulin resistance; these factors are associated with an adverse thrombo-inflammatory environment,¹⁰ and collectively and independently predict cardiovascular complications in this population.^{16,17} As such, it is plausible that interrupting prolonged sitting with activity breaks may elicit acute changes in the cardiovascular-inflammatory milieu. In people with and without T1D, inflammatory responses are typically exaggerated after acute physical activity but attenuated over time in response to regular physical activity.^{18–20} To the best of our

knowledge, no study has investigated the acute vascular-inflammatory response to intermittent light-intensity activity in T1D.

In this study, we aimed to characterize the impact of interrupting prolonged sitting with short, frequent, light-intensity walking activity on postprandial vascular-inflammatory markers in people with T1D.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The SIT-LESS study is a randomized crossover controlled trial that was undertaken between May 2021 and December 2022 at the University of Sunderland, UK; detailed information can be found elsewhere.¹⁵ Briefly, patients were eligible for inclusion if they were aged between 18 and 60 years with a duration of diabetes >2 years on enrolment with autoantibody-confirmed T1D treated on a stable (>6 months) insulin regimen consisting of continuous subcutaneous insulin infusion or multiple daily injections and classified as 'inactive' as per international physical activity guidelines (<150 min of moderate-vigorous intensity physical activity per week).²¹ Exclusion criteria were pregnancy, the presence of significant functional limitations, overt diabetes complications, or hypoglycaemia unawareness.

2.2 | Pre-experimental procedures

Following 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.²² Following this, patients underwent randomization to determine the order of two cross-over experimental arms; study personnel and participants were blinded to the

experimental condition order until the first experimental visit. Both arms consisted of a day-long laboratory visit, each of which commenced in the morning (approximately 08:00 h) and were separated by a minimum of 7 days.

Eligible participants then underwent initial study orientation and were instructed to record the diet and insulin regimen in a diary and were provided with a pedometer to record step count during the 48 h before and after the first experimental laboratory visit; these procedures ensured glycaemic stabilization and the replication of diet, insulin administration and physical activity levels during the second experimental period.¹⁵ Forty-eight hours before each experimental condition, participants were required to abstain from exercise, caffeine and alcohol. Standardized text messaging and/or email prompts were used to maximize participant compliance. On the evening before each experimental visit, a standardized mixed-macronutrient meal was consumed by participants, details of which have been described previously,¹⁵ thus allowing standardization of glycaemic control before experimental observation. After consuming the meal, participants were instructed to avoid further food intake, including beverages with substantial calories. In the instance of hyperglycaemia, participants were permitted to administer insulin boluses, and in the instance of hypoglycaemia, they consumed glucose supplements as prescribed. The aim was to ensure fasting status upon arrival at each experimental visit. Continuous glucose monitoring captured interstitial glucose concentrations across the entire study period.

2.3 | Experimental procedures

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-min bouts of self-paced light-intensity walking at 30-min intervals commencing 60 min after each meal, equating to a total of 36 min of physical activity across the 7-h period. 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.

Venous blood samples were obtained at baseline, 3.5 h and 7 h, and dispensed evenly into lithium-heparin tubes (Vacurette; Greiner Bio-One GmbH), which were centrifuged for 15 min at 1100g, and stored at -80°C for retrospective analysis of plasma levels of IL-1 β (human IL-1 β Quantikine ELISA; R&D Systems, Roche Diagnostics), TNF- α (human TNF- α Quantikine ELISA; R&D Systems, Roche Diagnostics), PAI-1 (human PAI-1/serpin ELISA kit DSE100; R&D Systems, Roche Diagnostics) and fibrinogen (ab108842, fibrinogen human ELISA Kit; Abcam), as previously described²³; high precision of the assays is evident by a coefficient of variation of <8%. An additional blood sample was taken at baseline on the first experimental arm for the determination of HbA1c (Tosoh HLC-723G8 Automated Glycohemoglobin Analyser).

2.4 | Data analysis

Two-way repeated measure analysis of variance (ANOVA) was used to determine within- and between-condition time-course changes in vascular-inflammatory parameters; Bonferroni corrections were applied to adjust for multiple comparisons. Moreover, the cohort was stratified based on insulin resistance status, using a prespecified estimated glucose disposal rate (eGDR) cut-point of <8 mg/kg/min for subgroup analysis.²⁴ To establish the magnitude of treatment response, we calculated the conditional difference in the average change from baseline in each biomarker; multiple linear regression was used to study the magnitude of treatment effect stratified by eGDR status. Statistical significance was accepted at a threshold of $p < .05$, and the data are presented as mean \pm SD. Our post-hoc power analysis showed >90% power across all parameters (TNF- α : 90.7%; IL-1 β : 91.3%; PAI-1: 93.0%; fibrinogen: 98.1%).

3 | RESULTS

3.1 | Patients

Thirty-two participants with T1D [age 27.9 ± 4.7 years, 15/17 men/women, body mass index 26.5 ± 3.5 kg/m², diabetes duration 16.0 ± 6.9 years, HbA1c $8.4 \pm 1.4\%$ (68 ± 2.4 mmol/mol); continuous subcutaneous insulin infusion vs. multiple daily injections, $n = 15$ vs. 17] were randomized and completed both experimental conditions.

TABLE 1 Vascular-inflammatory responses to SIT versus SIT-LESS.

	SIT	SITLESS	p-Value
Baseline			
TNF- α , pg/ml	3.67 ± 2.08	3.65 ± 2.13	NS
IL-1 β , pg/ml	4.08 ± 3.11	4.17 ± 3.03	NS
PAI-1, ng/ml	1.75 ± 0.94	1.68 ± 0.97	NS
Fibrinogen, g/L	3.25 ± 1.69	3.23 ± 1.69	NS
3.5 h			
TNF- α , pg/ml	4.34 ± 1.95	3.31 ± 1.91	<.001
IL-1 β , pg/ml	5.72 ± 4.08	3.95 ± 3.12	<.001
PAI-1, ng/ml	1.92 ± 1.09	1.38 ± 0.70	.002
Fibrinogen, g/L	3.90 ± 2.65	1.90 ± 1.24	<.001
7 h			
TNF- α , pg/ml	5.48 ± 1.68	2.83 ± 1.70	<.001
IL-1 β , pg/ml	6.80 ± 4.43	3.80 ± 3.03	<.001
PAI-1, ng/ml	2.61 ± 1.12	0.98 ± 0.38	<.001
Fibrinogen, g/L	5.25 ± 3.76	1.80 ± 1.33	<.001

Note: Data are presented as mean \pm standard deviation. Abbreviations: IL, interleukin; PAI, plasminogen activator inhibitor; SIT, uninterrupted sitting; SIT-LESS, interrupted sitting with 3-min bouts of self-paced light-intensity walking at 30-min intervals; TNF, tumour necrosis factor.

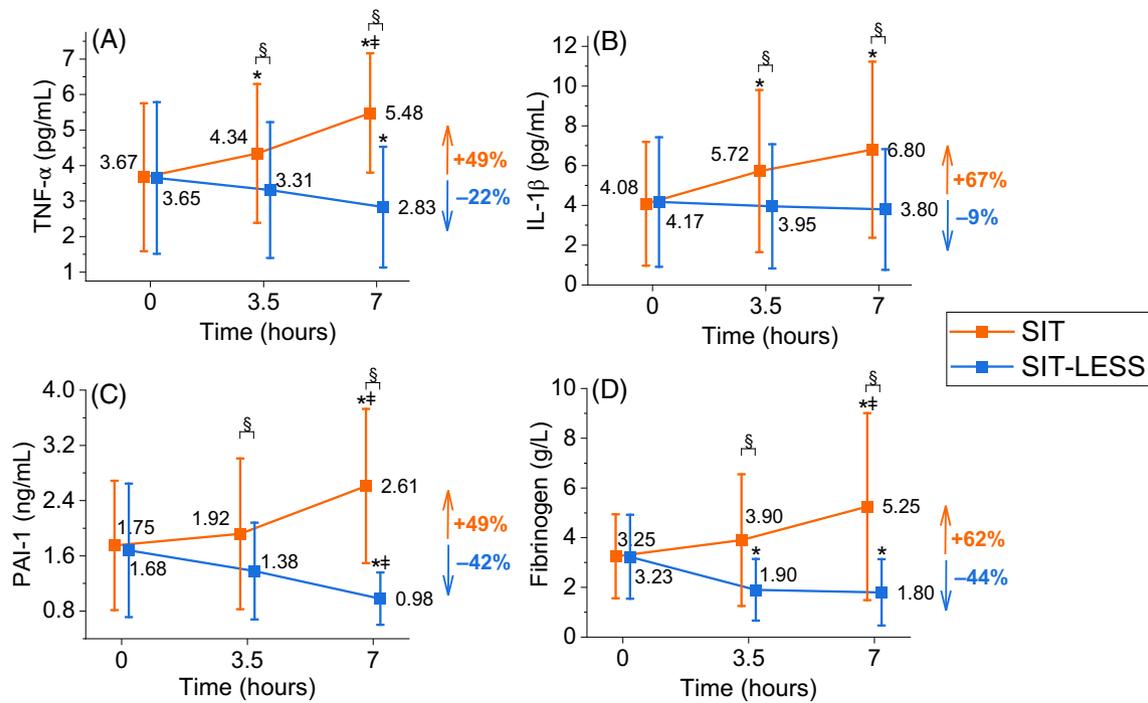


FIGURE 1 Temporal changes in vascular-inflammatory parameters and triglyceride concentrations under the SIT and SIT-LESS conditions. (A) TNF- α , (B) IL-1 β , (C) PAI-1, (D) fibrinogen. §Statistically significant between-condition difference at $p < .05$. *Statistically significant within-condition difference when compared with baseline at $p < .05$. ‡Statistically significant within-condition difference when compared with 3.5 h at $p < .05$. Data are presented as mean \pm SD. IL, interleukin; PAI, plasminogen activator inhibitor; SIT, uninterrupted sitting; SIT-LESS, interrupted sitting with 3-min bouts of self-paced light-intensity walking at 30-min intervals; TNF, tumour necrosis factor.

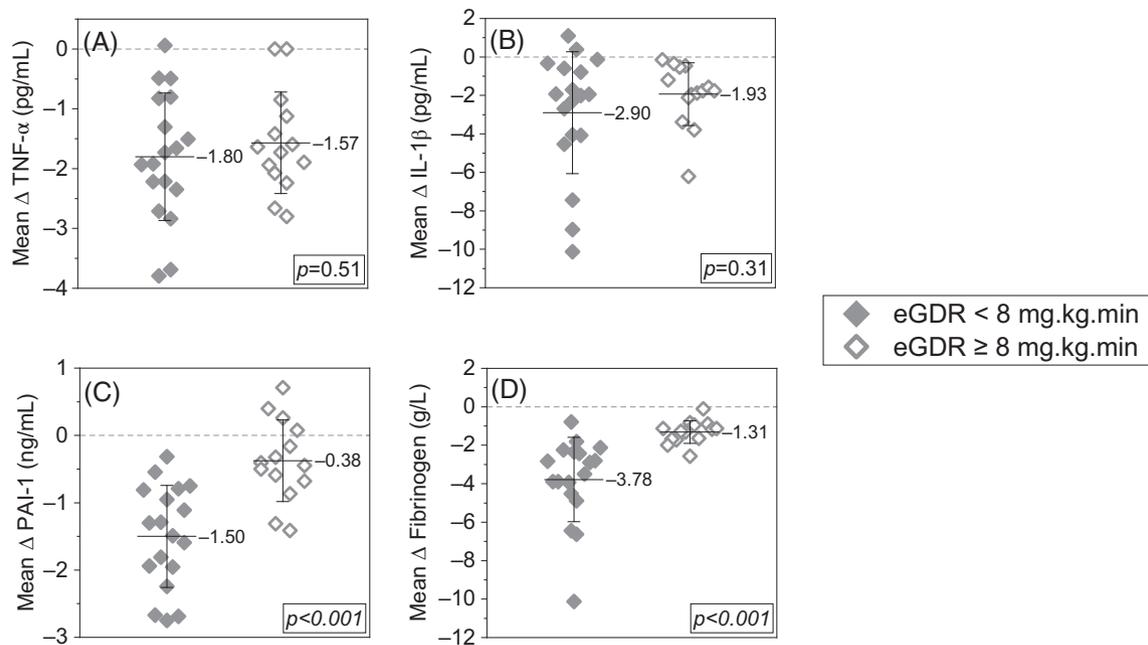


FIGURE 2 Individualized magnitude of change in treatment response between SIT and SIT-LESS across: (A) mean TNF- α , (B) mean IL-1 β ; (C) mean PAI-1, (D) mean fibrinogen. Treatment response calculated by subtracting mean SIT-LESS responses from mean SIT responses. $p < .05$ indicates statistical difference in treatment response. Data are presented as mean \pm SD. Filled diamonds, pre-treatment eGDR < 8 mg/kg/min; hollow diamonds, pre-treatment eGDR \geq 8 mg/kg/min; eGDR, estimated glucose disposal rate; IL, interleukin; PAI, plasminogen activator inhibitor; SIT, uninterrupted sitting; SIT-LESS, interrupted sitting with 3-min bouts of self-paced light-intensity walking at 30-min intervals; TNF, tumour necrosis factor.

3.2 | Interrupted sitting attenuates the postprandial rise in vascular-inflammatory biomarkers

Resting baseline vascular-inflammatory parameters were similar between SIT and SIT-LESS (TNF- α : SIT 3.67 pg/ml vs. SIT-LESS 3.65 pg/ml; IL-1 β : SIT 4.08 pg/ml vs. SIT-LESS 4.17 pg/ml; PAI-1: SIT 1.75 ng/ml vs. SIT-LESS 1.68 ng/ml; fibrinogen: SIT 3.25 g/L vs. SIT-LESS 3.23 g/L; $p > .1$ for all; Table 1).

In response to SIT, TNF- α , IL-1 β , PAI-1, and fibrinogen markedly increased over the observation window, whereas SIT-LESS attenuated these rises such that concentrations across all chosen variables were lower at 7 h (TNF- α : SIT + 49% vs. SIT-LESS -22%; IL-1 β : SIT + 67% vs. SIT-LESS -9%; PAI-1: SIT + 10% vs. SIT-LESS -42%; fibrinogen: SIT + 62% vs. SIT-LESS -44%; $p < .001$ for all; Figure 1A-D).

3.3 | Insulin resistance and glucose status impact the magnitude of the treatment response to interrupted sitting

Individuals with lower pre-treatment eGDR [<8 mg/kg/min; higher insulin resistance (IR) status] elicited a greater average reduction in PAI-1 (mean Δ -1.50 vs. -0.38 pg/ml; $p < .001$) and fibrinogen (mean Δ -3.78 vs. -1.31 g/L; $p < .001$) over the 7 h (Figure 2A-D).

IR status did not influence the change in TNF- α ($p > .05$) or IL-1 β ($p = .31$). eGDR inversely predicted a change in PAI-1 ($\beta = -0.24$, $F = 43.41$, $r^2 = 0.59$, $p < .001$) and fibrinogen ($\beta = -0.56$, $F = 42.72$, $r^2 = 0.59$, $p < .001$); similarly, eGDR status did not mediate the response in TNF- α or IL-1 β (Table 2). Increased pre-treatment HbA1c was associated with a greater average reduction in IL-1 β , PAI-1 and fibrinogen ($p < .05$; Table 2), but not TNF- α ($p > .05$; Table 2), whereas increased mean glucose levels were associated with greater reductions in TNF- α and fibrinogen ($p < .05$; Table 2), but not IL-1 β or PAI-1 ($p > .05$; Table 2). Glucose variability did not mediate the magnitude of change in any outcome variable.

4 | DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effect of interrupting prolonged sitting with short, frequent bouts of light-intensity walking activity on postprandial vascular-inflammatory mediators in people with T1D. Therefore, a simple lifestyle change can attenuate the postprandial rise in vascular-inflammatory biomarkers. This study extends recent experimental work showing improvements in acute glucose control in response to interrupted sitting,¹⁵ which collectively may reduce the risk of developing long-term diabetes complications if sustained.

TABLE 2 Association between eGDR, HbA1c, mean glucose levels and glucose variability with the magnitude of change in vascular parameters between SIT and SIT-LESS.

	β	95% CI	F-value	R ²	p-Value
By eGDR					
TNF- α	-0.076	-0.20, 0.047	1.60	0.051	.220
IL-1 β	-0.29	-0.61, 0.037	3.27	0.098	.081
PAI-1	-0.24	-0.31, -0.16	43.41	0.59	<.001
Fibrinogen	-0.56	-0.73, -0.38	42.72	0.59	<.001
By HbA1c					
TNF- α	0.12	-0.14, 0.38	0.87	0.028	.360
IL-1 β	0.84	0.20, 1.48	7.28	0.20	.011
PAI-1	0.47	0.31, 0.64	33.86	0.53	<.001
Fibrinogen	0.53	0.68, 1.48	30.51	0.50	<.001
By average glucose					
TNF- α	0.13	0.0082, 0.25	4.74	0.14	.037
IL-1 β	0.24	-0.11, 0.59	1.98	0.062	.170
PAI-1	0.071	-0.048, 0.19	1.50	0.048	.230
Fibrinogen	0.35	0.095, 0.60	7.89	0.21	.009
By glucose variability					
TNF- α	0.0052	-0.021, 0.032	0.16	0.0052	.690
IL-1 β	0.0089	-0.063, 0.081	0.064	0.0021	.800
PAI-1	-0.00037	-0.025, 0.024	0.00095	0.000032	.980
Fibrinogen	0.026	-0.030, 0.082	0.89	0.029	.350

Abbreviations: eGDR, estimated glucose disposal rate; HbA1c, glycated haemoglobin; IL, interleukin; PAI, plasminogen activator inhibitor; SIT, uninterrupted sitting; SIT-LESS, interrupted sitting with 3-min bouts of self-paced light-intensity walking at 30-min intervals; TNF, tumour necrosis factor.

Cardiovascular complications in T1D are driven by an enhanced inflammatory/thrombotic milieu and are characterized by raised levels and activities of procoagulant proteins as well as compromised function of the fibrinolytic system,⁴ thereby increasing the risk of vascular occlusive events. Plasma levels of prothrombotic, including fibrinogen, and antifibrinolytic factors, such as PAI-1, are increased in people with diabetes,^{10,11,25} particularly in T2D and T1D with associated IR.^{4,10,25} In the present study, postprandial fibrinogen increased by 61% and PAI-1 by 49% under SIT, showing the acute deleterious impact of prolonged sitting in this population. In contrast, simply interrupting prolonged sitting with activity breaks prevented the rise in postprandial fibrinogen and PAI-1 plasma levels. Similarly, TNF- α and IL-1 β increased in response to SIT, whereas the rise was completely attenuated in response to SIT-LESS. TNF- α and IL-1 β enhance NF- κ B activity, increasing adhesion molecule expression and subsequently aggravating inflammatory processes,^{26,27} thus contributing to vascular pathology.

Although T1D is believed to be a disease solely of progressive insulin deficiency, resistance to insulin appears to contribute to both microvascular and macrovascular complications in this population.¹⁶ Using eGDR,²⁸ a validated measure of insulin resistance, we found that the improvement in fibrinogen and PAI-1 was greater in those patients with increased IR and that IR was predictive of the change in fibrinogen and PAI-1. Given that IR is both prevalent in the general T1D patient population and heightened further in sedentary individuals with T1D,³ this simple intervention may prove to be a pragmatic solution to addressing increased vascular risk in a large proportion of T1D individuals.

The cross-over design is a strength of this study, enhancing the internal validity and reliability of findings and enabling control for between-subject factors across experimental exposures. We also employed a tightly controlled pre-experimental run-in phase to accommodate for several potential confounding variables known to affect vascular-inflammatory biomarkers. Study limitations include the single-centre nature of patients with T1D and the exclusion of those with overt complications. Furthermore, the study was originally powered to detect changes in glucose levels in response to the intervention,¹⁵ and therefore it is not clear whether it had enough power to detect changes in inflammatory markers. However, our post-hoc power calculations revealed that our sample size was sufficient to achieve 90% power to detect percentage changes across all of our chosen outcome variables. Given the short observation window of this study, we describe changes in acute vascular-inflammatory biomarkers, and further work is required to establish the exact mechanisms underpinning our findings. Further long-term outcome studies are required to investigate whether this intervention is effective at delaying the progression of established complications and whether such an intervention can be modified so that it can be applied remotely within the community.

5 | CONCLUSIONS

Interrupting prolonged sitting with short, frequent bouts of light-intensity walking activity attenuates the deleterious rise in

postprandial vascular-inflammatory parameters associated with prolonged sitting. The magnitude of improvement in these markers appears to be modulated by the presence of IR. Longer and larger studies are warranted to confirm these findings across a more diverse and representative sample of individuals with T1D.

AUTHOR CONTRIBUTIONS

NZS: visualization and writing (original draft, review and editing); AMA: investigation, visualization, writing (review and editing); MH: investigation, visualization, writing (review and editing); PC: 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); MDC: 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.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15564>.

DATA AVAILABILITY STATEMENT

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.

ORCID

Nawaz Z. Safdar  <https://orcid.org/0000-0002-4232-7146>

Sam M. Pearson  <https://orcid.org/0000-0002-4943-6759>

Noppadol Kietsiriroje  <https://orcid.org/0000-0002-5076-4450>

Matthew D. Campbell  <https://orcid.org/0000-0001-5883-5041>

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