FULL TITLE: HIT IMPROVES AEROBIC CAPACITY WITHOUT A DETRIMENTAL DECLINE IN BLOOD GLUCOSE IN PEOPLE WITH TYPE 1 DIABETES

PRECIS: Six weeks of HIT improves aerobic capacity and aortic pulse wave velocity to a similar extent to MICT in people with type 1 diabetes without a detrimental decline in blood glucose concentration

SHORT TITLE: HIT in people with type 1 diabetes

Sam N. Scott[1]; Matt Cocks[1]; Rob C. Andrews[2]; Parth Narendran[3]; Tejpal S. Purewal[4]; Daniel J. Cuthbertson[5]; Anton J. M. Wagenmakers[1] & Sam O. Shepherd[1]

[1]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

[2]University of Exeter, Exeter, UK

[3]University of Birmingham, Birmingham, UK

[4]Royal Liverpool & Broadgreen University Hospital, Liverpool, UK

[5]Obesity and Endocrinology Research Group, University of Liverpool, UK

Corresponding author:

Sam Shepherd

S.Shepherd@ljmu.ac.uk

Research Institute for Sport and Exercise Sciences, Tom Reilly Building, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF

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ABREVIATIONS

HIT – High intensity interval training

MICT – Moderate intensity continuous training

CON – Control day of no exercise

aPWV – Aortic pulse wave velocity

CGMS – Continuous glucose monitoring system

CHO - Carbohydrate

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

MAP – Mean arterial pressure

EXTOD – Exercising for type 1 diabetes

$\dot{V}O_{2max}$ – Aerobic capacity

W_{max} – Maximal power output

$\dot{V}O_{2peak}$ - Peak oxygen consumption

IMTG - Intramuscular triglyceride

DISCLOSURE SUMMARY

The authors have no conflicts of interest to disclose.

ABSTRACT

AIMS – To investigate whether 1) six weeks of high-intensity interval training (HIT) induces similar improvements in cardio-metabolic health markers as moderate-intensity continuous training (MICT) in people with type 1 diabetes, and 2) whether HIT abolishes acute reductions in plasma glucose observed following MICT sessions.

METHODS – Fourteen sedentary individuals with type 1 diabetes (*n*=7 per group) completed six weeks of HIT or MICT 3 times per week. Pre- and post-training measurements were made of 24h interstitial glucose profiles (using continuous glucose monitors (CGMS)) and cardio-metabolic health markers ($\dot{V}O_{2peak}$, blood lipid profile and aortic pulse wave velocity; aPWV). Capillary blood glucose concentrations were assessed before and after exercise sessions throughout the training programme to investigate changes in blood glucose during exercise in the fed state.

RESULTS – Six weeks of HIT or MICT increased $\dot{V}O_{2peak}$ by 14% and 15%, respectively (P<0.001), and aPWV by 12% (P<0.001), with no difference between groups. 24h CGMS data revealed no differences in incidence or percentage of time spent in hypoglycaemia following training in either group (P>0.05). In the fed state, the mean change in capillary blood glucose concentration during the HIT sessions was -0.2±0.5 mmol/L, whereas blood glucose change was -5.5±0.4 mmol/L during MICT.

CONCLUSIONS - Six weeks of HIT improved $\dot{V}O_{2peak}$ and aortic PWV to a similar extent as MICT. The finding that blood glucose remained stable during HIT in the fed state, but consistently fell during MICT, suggests that HIT may be the preferred training mode for some people with type 1 diabetes.

INTRODUCTION

Regular exercise is recommended for people with type 1 diabetes to maintain overall health and reduce the risk of macrovascular and microvascular complications, which are a major cause of mortality and morbidity[1,2]. The current guidelines for people with type 1 diabetes are to undertake at least 150 minutes of moderate to vigorous aerobic exercise per week, spread over at least three days per week, with no more than two consecutive days without activity[3]. Benefits of exercise for those with type 1 diabetes include improved aerobic capacity ($\dot{V}O_{2max}$), insulin sensitivity, body composition, endothelial function and blood lipid profile[1,4-6]. Despite the benefits, few people with type 1 diabetes achieve exercise targets and many programmes designed to increase physical activity have failed[7,8]. In addition to the barriers to exercise cited by the general population, such as a perceived lack of time, work commitments and cost[9], people with type 1 diabetes face additional barriers including fear of hypoglycaemia, loss of glycaemic control and inadequate knowledge around exercise management[10,11].

To overcome a perceived lack of time, high intensity interval training (HIT) is purported as a time-efficient alternative to moderate-intensity exercise to improve numerous cardio-metabolic risk factors including $\dot{V}O_{2max}$, insulin sensitivity and glycaemic control in people without type 1 diabetes[12,13]. Furthermore, results from our laboratory show that a single bout of HIT does not increase the risk of hypoglycaemia in people with type 1 diabetes (Scott et al. unpublished observations, see supplementary material[14]). Whether HIT offers a safe, effective and time-efficient training strategy to improve cardio-metabolic health that reduces the risk of hypoglycaemia in people with type 1 diabetes is yet to be investigated.

Here we investigated the hypothesis that six weeks of HIT would improve markers of cardio-metabolic health, including $\dot{V}O_{2peak}$, glycaemic control, blood lipid profile and vascular health in people with type 1 diabetes. A moderate intensity continuous training (MICT) group was used as a control. During this 6-week training period capillary blood glucose concentrations were monitored before and after exercise sessions to provide further information on the acute effects of HIT and MICT on blood glucose concentration.

RESEARCH DESIGN AND METHODS

Fourteen previously sedentary people with type 1 diabetes (10 men/4 women; see Table 1 for participant characteristics) on a basal-bolus insulin regimen completed six weeks of supervised HIT (*n*=7) or MICT (*n*=7) three times per week. Participants were pair-matched based on sex, age and $\dot{V}O_{2peak}$ to the two training groups. Exclusion criteria were duration of type 1 diabetes <6 months, insulin pump therapy, poor diabetes control (HbA1c >86 mmol/mol), frequent hypoglycaemia (>5 per week) and/or hypo-unawareness (determined from medical history), obesity (BMI >30 $kg \cdot m^{-2}$), pregnancy or planning pregnancy, uncontrolled hypertension (>180/100 mmHg), angina, autonomic neuropathy, taking any medication that affects heart rate, major surgery planned within 6 weeks of the study, severe nonproliferative and unstable proliferative retinopathy. Testing took place in the laboratory of the School of Sport and Exercise Sciences at Liverpool John Moores University. The study was approved by the Black Country NHS Research Ethics Committee (West Midlands, UK) and all participants gave written informed consent to a protocol conforming to the *Declaration of Helsinki*.

Pre-training assessments

Participants first performed an incremental exercise test to exhaustion on an electromagnetically braked cycle ergometer (Excalibur Sport V2.0, Lode, Groningen, The Netherlands) to determine maximal aerobic power output (W_{max}) and $\dot{V}O_{2peak}$ using an online gas collection system (MOXUS modular oxygen uptake system, AEI technologies, Pittsburgh, PA). The test consisted of 3-minute stages starting at 60 W, and the workload was increased by 35 W at each stage until subjects could not maintain a cadence of >50 rpm, at which point the test was terminated. $\dot{V}O_{2peak}$ was taken as the highest value achieved over a 15 second recording period. Participants also completed a food diary over a minimum of three days in order to calculate habitual caloric and macronutrient intake.

Three to 7 days after the incremental exercise test, participants attended the laboratory after an overnight fast (>10 h) for a second pre-training assessment session. Following 15 minutes rest, supine brachial artery blood pressure measurements were made in triplicate using an automated sphygmomanometer (GE DINAMAP Pro 300 V2). Aortic pulse wave velocity (aPWV) measurements were made using a semi-automated device and software (SphygmoCor, AtCor Medical, Sydney, Australia), as previously described by Cocks et al.[15]. A fasting blood sample was used to determine fasting plasma cholesterol and triglyceride concentrations, using a semi-automatic spectrophotometer (Randox RX Daytona™, County Antrim, UK).

A Dexcom G4 Platinum (Dexcom, San Diego, CA, USA) CGMS probe was inserted subcutaneously into the abdomen. A habitual free-living 24h glucose profile was analysed at least 24 hours after the CGMS was inserted. Participants were

trained to use the CGMS and instructed to calibrate the device a minimum of four times daily using capillary blood tests. Participants were provided with a standardised diet of three meals (breakfast, lunch and dinner) during the CGMS period (50% CHO; 30% fat; 20% protein) in accordance with their habitual calorie intake. Participants were instructed to consume these meals at pre-determined time points throughout the day. No additional snacks were permitted and participants only consumed the food provided by the research team during this period, unless they needed to prevent hypoglycaemia (blood glucose <3.0 mmol/L)[16]. A food diary was completed to confirm that they had consumed the prescribed food at the correct times. Participants were instructed to avoid alcohol and caffeine, as well as exercise throughout the CGMS period.

Exercise Training

Training started ~72h after completion of the pre-experimental procedures. Participants trained three times per week for six weeks under researcher supervision on a Lode Corival cycle ergometer (Corival Lode BV, Groningen, The Netherlands). Following a 3-minute low-intensity warm-up, the HIT group performed repeated 1-minute bouts of high intensity cycling at a workload equivalent to 100% $\dot{V}O_{2peak}$ interspersed with 1 minute of recovery at 50 W, whereas the MICT group performed continuous moderate intensity cycling at a workload equivalent to 65% $\dot{V}O_{2peak}$. The number of intervals in the HIT group increased from 6 in weeks 1 and 2, to 8 in weeks 3 and 4 to 10 in weeks 5 and 6. The duration of the sessions in the MICT group were 30 minutes in weeks 1 and 2, 40 minutes in weeks 3 and 4 and 50 minutes in weeks 5 and 6.

Acute change in blood glucose with exercise

Participants were able to attend their training session between 7am and 5pm Monday to Friday. The amount and type of food was not controlled but we asked participants not to fast before exercising and not to exercise within 30 minutes of a meal with the aim being to study the effects of HIT and MICT under 'real world' conditions. Therefore, these training sessions are defined as being in the 'fed' state in this investigation. In line with advice that has been used in other studies[17], and in keeping with international agreed advice[18], if patients were doing MICT within 2 hours of a meal they were asked to reduce their fast acting insulin at that meal by 50%. No adjustments were made if doing a HIT session. Before starting and after completing each training session during the six-week training period, participant's blood glucose concentrations were required to be between 7-14 mmol/L. If blood glucose concentrations fell outside of this range corrective measures were taken; glucose was ingested if blood glucose <7 mmol/L, and a light walk or insulin bolus was advised if glucose >14 mmol/L, as well as checking blood ketones. In addition, when they first started exercising they were asked to check their glucose at 2am and to reduce their night time background insulin by 10%. Reduction of insulin at night could be continued if the participant found that their glucose was going low overnight on the day of exercise. All participants were asked to measure their blood glucose before and after an exercise session, in addition participants in the MICT arm were advised to check their blood glucose part-way through the exercise and to consume carbohydrate as necessary to prevent hypoglycaemia. Over the course of the 6 weeks of training we gathered pre and post-exercise blood glucose concentrations from a total of 108 (86%) MICT training sessions and 87 (69%) HIT sessions.

204 **Post-training assessments**

205 Approximately 72h after the final training session, participants attended the
206 laboratory on two occasions (separated by 72h) to complete a series of post-training
207 assessments. These assessments were identical in all respects to those undertaken
208 prior to training (pre-training assessments).

209

210 **Statistical analyses**

211 The primary outcome variable to measure a significant training benefit was $\dot{V}O_{2peak}$.
212 Previous research in our group[17,19] has suggested a SD of 2.7-3.2 to detect a
213 change in $\dot{V}O_{2peak}$ of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$, which is a clinically significant increase in
214 $\dot{V}O_{2peak}$[20]. A power calculation suggested that 7-9 participants were required in each
215 group to detect a within-group difference with a paired *t* test with 80% power at a
216 significance level of 0.05. Continuous glucose monitor data were downloaded from
217 the device using Dexcom Studio™ software (12.0.4.6) and analysed in accordance
218 with the International Consensus on Use of Continuous Glucose Monitoring[21].
219 Glycaemic thresholds were defined as follows: target range (3.9-10 mmol/L), level 1
220 hypoglycaemia (≤3.9 mmol/L), level 2 hypoglycaemia (≤2.9 mmol/L) and
221 hyperglycaemia (≥10 mmol/L). The 24h period was defined as 08:00-08:00h and the
222 nocturnal period was defined as 24:00-06:00h. All variables were analysed using a
223 two-way mixed ANOVA, with the between factor 'group' (HIT vs. MICT) and repeated
224 factor 'training status' (pre-training vs. post training), followed by Bonferroni *post-hoc*
225 corrections. A two way mixed ANOVA, with the between factor 'group' and the
226 repeated factor 'time point' (pre-training vs. post training) was used to assess
227 whether there was an acute change in blood glucose concentration following HIT
228 and MICT in the fed state over the 6 weeks of training. The CGMS did not work on

one participant in the MICT group. Aortic PWV readings were obtained from five participants in the HIT group and six in the MICT group. All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Data are presented as mean ± SEM and significance was set at $P \leq 0.05$.

RESULTS

By design, there were no differences in age ($P=0.877$), $\dot{V}O_{2peak}$ ($P=0.371$) or duration of type 1 diabetes ($P=0.291$) between the training groups at baseline. BMI was, however, significantly higher in the HIT group compared to the MICT group ($P=0.038$). Pre and post-training variables are presented in Table 1. Training increased $\dot{V}O_{2peak}$ (HIT 14%, MICT 15%; $P<0.001$) and W_{max} (HIT 13%, MICT 14%; $P<0.001$), with no difference between groups (Fig. 1). Six weeks of training also improved aPWV ($P=0.001$) and there was no difference between groups. Systolic, diastolic and mean arterial blood pressure did not improve following training ($P=0.219$; $P=0.476$; $P=0.268$, respectively). There was no change in plasma cholesterol or triglyceride concentrations with training ($P=0.881$; $P=0.652$, respectively).

Glycaemic control

Glucose data from the CGMS obtained over a 24h period pre- and post-training are presented in Table 2. There was no difference in the time spent in level 1 hypoglycaemia (≤3.9 mmol/L) over the 24h period ($P=0.727$) or nocturnal period ($P=0.289$) with training. Similarly, there was no difference in time spent in level 2

hypoglycaemia (≤2.9 mmol/L) with training over the 24h period (*P*=0.442) or nocturnal period (*P*=0.397). There were also no differences in the time spent in target range over the 24h (*P*=0.412) or nocturnal periods (*P*>0.382). Furthermore, there was no difference in the time spent in hyperglycaemia over the 24h (*P*=0.540) or nocturnal period (*P*=0.118). However, there was an interaction effect for the time spent in target range (*P*=0.034) and time in hyperglycaemia over the nocturnal period (*P*=0.039). Post hoc analysis revealed that the HIT group spent significantly less time in target glycaemia during the nocturnal period (*P*=0.038) which was due to a greater time spent in hyperglycaemia over the nocturnal period (*P*=0.016). The incidence of level 1 hypoglycaemia over the 24h period (*P*=0.675) and nocturnal period (*P*=0.363) was no different before and after HIT or MICT. There were no differences in the incidence of level 2 hypoglycaemia over the 24h (*P*=0.174) or nocturnal (*P*=0.549) period following 6 weeks of HIT or MICT.

Acute change in blood glucose during training sessions

When quantifying the change in blood glucose concentration during exercise training sessions undertaken in the fed state over the six-week intervention, the mean change in blood glucose concentration in response to HIT was -0.2 ± 0.5 mmol/L (*P*<0.001) whereas blood glucose decreased by -5.5 ± 0.4 mmol/L in response to MICT (*P*=0.626; Fig. 2).

DISCUSSION

This study demonstrates for the first time that six weeks of HIT improves $\dot{V}O_{2peak}$ and aPWV in people with type 1 diabetes to a similar magnitude as MICT. Secondly, we observed that blood glucose concentration remained stable during the HIT sessions performed in the fed state throughout the training programme, but there was a consistently large drop in blood glucose during MICT throughout the training programme, with participants at risk of hypoglycaemia. The CGMS data revealed that 24 hour glucose was not affected by either form of training. However, overnight there was a decrease in the time spent in target range in the HIT group, due to an increase in time spent in hyperglycaemia, while there were no changes in glycaemic control in the MICT group. The fact that HIT is a time-efficient training mode that improved $\dot{V}O_{2peak}$ and aPWV to a similar extent as MICT but did not cause a fall in glucose during exercise as was observed during MICT means that it may be a more practical exercise strategy for some patients with type 1 diabetes. However, the increase in nocturnal hyperglycaemia following HIT is of concern and suggests that people with type 1 diabetes may have to reduce their carbohydrate intake prior to and/or following HIT sessions or make changes to their night-time background insulin to prevent high glucoses overnight.

Aerobic capacity improved to a similar extent following six weeks of HIT and MICT, despite the weekly time commitment being 54-90 minutes less for HIT than for MICT. The 14% increase in $\dot{V}O_{2peak}$ observed in our investigation following HIT (a mean increase of 4.9 $ml \cdot kg^{-1} \cdot min^{-1}$) is high in comparison to other studies using similar protocols that tend to report changes of 7-10% in populations without type 1 diabetes[22] and the only other study to examine the effect of sprint interval training in people with type 1 diabetes (repeated 30-second maximal cycling bouts interspersed with 3-4 minutes of rest 3 times a week for 7 weeks) reported a 7% increase in

299 $\dot{V}O_{2peak}$[23]. This has clinical importance given that $\dot{V}O_{2max}$ is reported to be the
300 strongest prognostic marker of cardiovascular mortality[20] and improvements
301 in $\dot{V}O_{2max}$ with exercise training are associated with a reduction in all-cause mortality
302 risk[24]. In fact, Myers[20] found that there is a 8-17% reduction in all-cause mortality for
303 each 1-MET (~3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) increase in $\dot{V}O_{2max}$. Although these correlations
304 have not been specifically confirmed in people with type 1 diabetes, it is likely that
305 the HIT programme used here induces clinically meaningful benefits to this
306 population, which is especially important as they are at increased risk of
307 cardiovascular disease compared to a non-diabetic population[1,2].

308 In the present study there was a 12% reduction in aPWV following both
309 training modes, which is greater than has previously been reported in other training
310 studies in populations without type 1 diabetes[25,26]. To the authors' knowledge, this is
311 the first study to investigate changes in arterial stiffness following HIT and MICT in
312 people with type 1 diabetes. The reduction in aPWV is of clinical relevance as
313 increased arterial stiffness is associated with negative cardiovascular outcomes[27].

314 Neither training mode improved glycaemic control according to the CGMS
315 data, measured as time spent in target range (euglycaemia) or hypoglycaemia or the
316 incidences of hypoglycaemia. Previous studies using HbA1c and daily insulin dosage
317 as a marker of glycaemic control have also failed to show overall improvements in
318 glycaemic control with exercise training[23,28,29], although studies reporting positive
319 effects of training on glycaemic control do exist[30]. There was a reduction in the time
320 spent in euglycaemia overnight in the HIT group which was due to an increase in the
321 time spent in hyperglycaemia. Although increasing the proportion of time spent in
322 hyperglycaemia during the nocturnal period is not desirable, it did reduce the risk of
323 developing hypoglycaemia which may mean that HIT is a preferable form of training

for those concerned about hypoglycaemia during exercise. The increased time spent in hyperglycaemia overnight with HIT is concerning, given that this will increase the risk of long term complications so needs to be explored further in the future. There are three potential reasons for this rise in glycaemia with HIT. Firstly, due to an increase in adrenaline and noradrenaline post exercise. However, although this may explain the higher glucose levels just after exercise, this is unlikely to explain the higher nocturnal glycaemia as these hormones fall rapidly after cessation of exercise. This is further supported by another study performed in our laboratory (Scott et al. under review in JCEM), that used CGMS to show that an acute bout of HIT did not increase glucose post exercise or in the overnight period. A second reason may be that participants consumed too much carbohydrate in the HIT condition as the total workload of HIT is less than MICT meaning that less glucose is removed from the blood to replenish muscle and liver glycogen stores. Thirdly, there may have been inadequate background insulin overnight. At the start of training, participants were asked to reduce their overnight background insulin by 10%. Thereafter, whether they did this was dependent on their blood glucose concentration before they went to bed, their blood glucose on the previous days after training, and how concerned they were about going low overnight. It may be that participants reduced their overnight background insulin when this was not required. Unfortunately, we did not record their insulin dosages so do not know if this happened. Although the use of CGMS in our investigation allowed a detailed analysis of glycaemic control, we acknowledge that longer duration exercise training programmes with larger sample sizes are needed to assess the effects of exercise training on long-term glycaemic control. Furthermore, the current guidelines suggest that a minimum of 14 consecutive days should be

348 recorded when analysing CGMS data[21]. Unfortunately, these guidelines were
349 published after our data collection was completed so will be used in future studies.

350 Before the training sessions, we recorded blood glucose concentration for
351 safety reasons to prevent participants from exercising when glucose concentrations
352 were too high or low based on the EXTOD guidelines[31]. Blood glucose was also
353 recorded after the sessions so that participants did not leave the laboratory while
354 they were potentially at increased risk of hypoglycaemia. This meant that we
355 collected pre and post-exercise blood glucose readings from up to 18 training
356 sessions for each participant over the course of six weeks of HIT or MICT. We
357 collected pre and post-exercise blood glucose concentrations from a total of 108
358 (86%) MICT training sessions and 87 (69%) HIT sessions. During the HIT sessions
359 glucose remained stable throughout the training programme whereas during MICT
360 sessions there was a consistently large fall in glucose. This was a consistent
361 observation across all participants undertaking MICT (Fig. 2b). Readings from at
362 least 9 sessions were available for every participant and the clear differences
363 between the groups and the low standard deviation for the changes in blood glucose
364 suggest the results were not affected by the different number of readings per group.
365 The changes in blood glucose concentration during the exercise reported here are
366 striking and are the first of their kind in the literature over so many training sessions.
367 Furthermore, they are supported by Garcia-Garcia et al.[32] who conducted a
368 systematic review and meta-analysis in which they aggregated results from 10
369 studies to estimate rate of change of glucose concentration during and after different
370 types of exercise in people with type 1 diabetes. Their results showed a rapid decline
371 in glycaemia during continuous exercise (-4.43 mmol/L h^{-1} on average) while the

results were more variable during intermittent high intensity exercise depending on the protocol.

The drop in blood glucose concentration during the MICT sessions is likely due to the effects of short-acting insulin in the circulation. In healthy individuals, blood glucose concentration remains stable during moderate-intensity aerobic exercise because insulin secretion is suppressed progressively with exercise duration and there is a gradual increase in glucagon and adrenaline resulting in increased hepatic glucose production[33,34]. Therefore, contraction-mediated glucose uptake is matched by increased hepatic glucose production so that blood glucose concentration remains stable at ~4.0-6.0 mmol/L[33]. However, as insulin is supplied exogenously in people with type 1 diabetes, hyperinsulinaemia is likely to occur because of increased blood flow and mobilisation of insulin from its subcutaneous depot, particularly if the injection site is in an exercised region[33]. This results in enhanced glucose uptake due to combined contraction-mediated and insulin-stimulated GLUT4 translocation. The high insulin levels will also suppress the exercise-mediated increases in glucagon and adrenaline and their ability to stimulate hepatic glucose production[35]. As a result, muscle glucose uptake during MICT will exceed hepatic glucose production, leading to the large decreases in plasma glucose concentration observed in this study (Fig. 2). Hyperinsulinaemia has also been shown to suppress adipose tissue and intramuscular triglyceride (IMTG) lipolysis in healthy individuals[36], which will reduce the contribution of lipids to the fuel mixture oxidised during exercise. The combination of insulin and exercise-mediated glucose disposal coupled with decreased hepatic glucose production and reduced lipolysis and lipid oxidation increases the risk of hypoglycaemia during MICT. On the other hand, the stable blood glucose concentrations following HIT are likely due to

greater plasma catecholamine (particularly noradrenaline) concentrations which lead to an increase in hepatic glucose production, thus offsetting the effects of hyperinsulinaemia[37]. Previous research has shown that addition of a sprint to a bout of moderate-intensity exercise in individuals with type 1 diabetes opposed the fall in glycaemia during exercise and this was associated with a rise in catecholamines[38]. Following a bout of HIT, it may be speculated that the greater catecholamine response compared to MICT may lead to stimulation of adipose tissue lipolysis and increase oxidation of the released fatty acids in the muscle during recovery[39].

Another important observation, although not quantitatively reported here, was the number of training sessions in which participants had to prevent or treat an episode of hypoglycaemia by consuming fast-acting carbohydrate. During the MICT sessions, participants were advised to stop exercising at least once to check their blood glucose concentration in accordance with the EXTOD guidelines[31], correct accordingly with glucose if necessary, and then wait for their blood glucose to stabilise before recommencing the training. Many of the participants in the MICT condition found this frustrating and it would often mean that the already time consuming 50-minute cycling sessions were even longer while blood glucose was checked. The large drop in blood glucose concentration that we found during the MICT sessions highlights why the guidelines recommend that carbohydrate should be taken when doing more than 30 minutes of moderate-intensity exercise[40]. Therefore, these findings provide evidence that HIT may be a more practical form of exercise for people with type 1 diabetes that regularly experience problems with hypoglycaemia during exercise.

The main strengths of this investigation were 1) the strict dietary standardisation under free-living conditions during the CGMS period pre and post-

training, and 2) the monitoring of acute changes in blood glucose concentrations during exercise throughout the intervention. We also acknowledge that there are some limitations. The sample size of the study was small; however, the clear significant increases in $\dot{V}O_{2peak}$ suggest that we have the power to conclude that HIT is effective at improving $\dot{V}O_{2peak}$ in people with type 1 diabetes. Secondly, we did not record insulin dose before and after the training intervention. This would be useful to determine whether there is a change in insulin sensitivity as reduced insulin dosage is associated with decreased risk of cardiovascular complications in people with type 1 diabetes[41,42].

In summary, this is the first study to demonstrate that six weeks of HIT leads to comparable improvements in $\dot{V}O_{2peak}$ and arterial stiffness to MICT. HIT though may be the preferred exercise approach, as blood glucose remains stable during HIT, but falls substantially during MICT. We therefore recommend that HIT in the fed state is a safe, effective, flexible and time-efficient form of exercise for people with type 1 diabetes.

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Registration

This study was registered as a clinical trial retrospectively in accordance with journal policy. ClinicalTrials.gov ID: NCT03544684.

CONTRIBUTION STATEMENT

SNS, MC, SOS, RCA, PN, DJC, TSP: conception and design of the experiments. SNS, MC, SOS, RCA, PN: collection, analysis and interpretation of the data. SNS, MC, SOS, RCA, PN, AJMW: drafting and revising the manuscript. All authors have read and approved the final manuscript. SOS is the guarantor for the article. The authors have no conflicts of interest to disclose.

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606 **Table 1** - General characteristics

	HIT		MICT	
	Pre	Post	Pre	Post
Age (years)	29 ± 3	-	29 ± 5	-
Sex	5M/2F	-	5M/2F	-
Duration of T1D (years)	13 ± 3	-	9 ± 2	-
Mass (kg)	90.0 ± 4.8	89.8 ± 4.8	76.7 ± 5.4	76.3 ± 5.3
BMI ($kg \cdot m^{-2}$)	29.2 ± 1.2	29.2 ± 1.2	25.3 ± 1.2	25.2 ± 1.2
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	35.6 ± 2.6	40.5 ± 2.6*	32.1 ± 2.6	36.9 ± 3.2*
$\dot{V}O_{2peak}$ (L/min^{-1})	3.2 ± 0.3	3.7 ± 0.3*	2.5 ± 0.3	2.9 ± 0.4*
Wmax (W)	245 ± 16	277 ± 19*	202 ± 22	231 ± 24*
SBP (mmHg)	121 ± 3	119 ± 4	123 ± 4	122 ± 4
DBP (mmHg)	65 ± 3	63 ± 3	70 ± 5	68 ± 4
MAP (mmHg)	84 ± 3	82 ± 2	87 ± 4	86 ± 3
aPWV (m/s)	6.1 ± 0.5	5.4 ± 0.7*	6.1 ± 0.4	5.4 ± 0.4*
Cholesterol (mmol/L)	5.07 ± 0.29	5.12 ± 0.35	4.81 ± 0.41	4.93 ± 0.41
Triglycerides (mmol/L)	0.94 ± 0.09	1.03 ± 0.25	0.70 ± 0.04	0.65 ± 0.06

607

608 BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood
609 pressure; MAP = mean arterial pressure; aPWV = arterial pulse wave velocity. Data
610 are presented as mean ± SEM. *Denotes a significant change from pre-training to
611 post-training ($P<0.05$).

612 **Table 2** - Summary of continuous glucose monitor data

	HIT		MICT	
	Pre	Post	Pre	Post
24h period				
Mean glucose (mmol/L)	9.3±0.3	9.5±1.0	9.2±0.6	8.6±0.7
CV (%)	42.6±3.6	38.2±2.6	37.9±3.6	36.9±4.0
Time in level 1 hypoglycaemia (%)	6.1±2.6	5.4±3.1	3.4±1.5	2.8±1.9
Time in level 2 hypoglycaemia (%)	0.2±0.2	0.5±0.3	0.9±0.5	0.0±0.0
Time in range (%)	56.7±3.1	56.4±7.8	59.3±5.8	68.2±7.7
Time in hyperglycaemia (%)	37.0±2.0	37.7±8.9	36.3±6.5	28.9±8.5
Incidence of level 1 hypoglycaemia	1.8±0.6	1.2±0.5	0.9±0.5	1.4±0.6
Incidence of level 2 hypoglycaemia	0.2±0.2	0.2±0.2	0.4±0.2	0.1±0.1
Incidence of hyperglycaemia	3.0±0.5	2.8±0.5	3.2±0.5	2.5±0.5
Nocturnal period				
Mean glucose (mmol/L)	8.8±1.3	11.7±2.0	8.0±1.2	7.4±1.1
CV (%)	23.2±5.9	19.5±9.1	29.1±7.2	22.2±6.2
Time in level 1 hypoglycaemia (%)	9.3±9.0	3.0±2.0	7.6±5.0	4.9±4.9
Time in level 2	0.0±0.0	1.2±1.2	3.2±2.0	0.0±0.0

hypoglycaemia (%)				
Time in range (%)	57.4±15.5	32.6±14.3*	60.0±15.4	71.3±16.5
Time in hyperglycaemia (%)	33.3±16.7	63.0±16.3*	28.5±15.9	23.6±15.8
Incidence of level 1 hypoglycaemia	0.5±0.2	0.3±0.2	0.3±0.2	0.1±0.1
Incidence of level 2 hypoglycaemia	0.0±0.0	0.2±0.2	0.3±0.2	0.0±0.0
Incidence of hyperglycaemia	0.5±0.2	0.8±0.2	0.5±0.2	0.3±0.2

The 24h period was defined as 08:00-08:00h and nocturnal period as 24:00-06:00h. Level 1 hypoglycaemia (≤3.9 mmol/L), level 2 (severe) hypoglycaemia (≤2.9 mmol/L), target range (3.9-10 mmol/L) and hyperglycaemia (≥10 mmol/L). There were no differences in any of the variables with training (P>0.05).

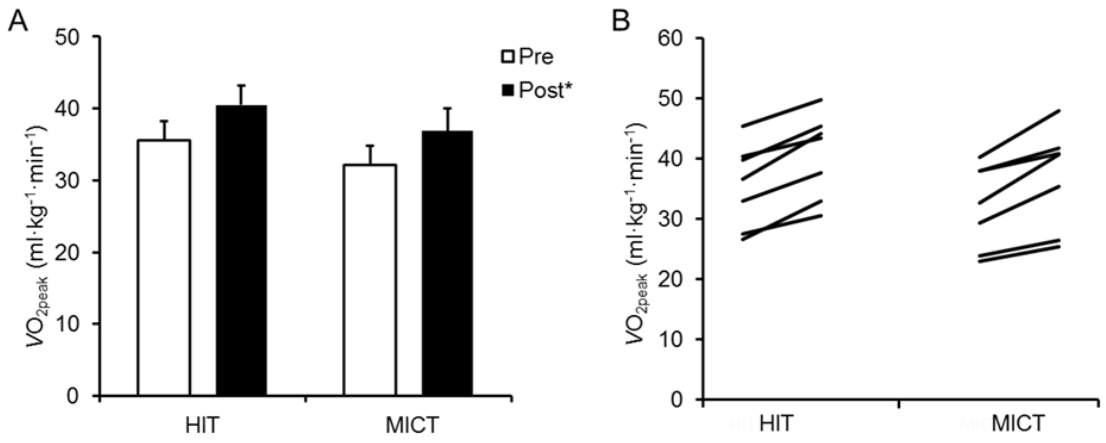

Figure 1 – Effect of six weeks of high intensity interval training (HIT) and moderate intensity continuous training (MICT) on $\dot{V}O_{2peak}$.

(A) Shows the mean responses and (B) shows individual responses in $\dot{V}O_{2peak}$ with training. *Indicates a significant difference from baseline (P<0.05).

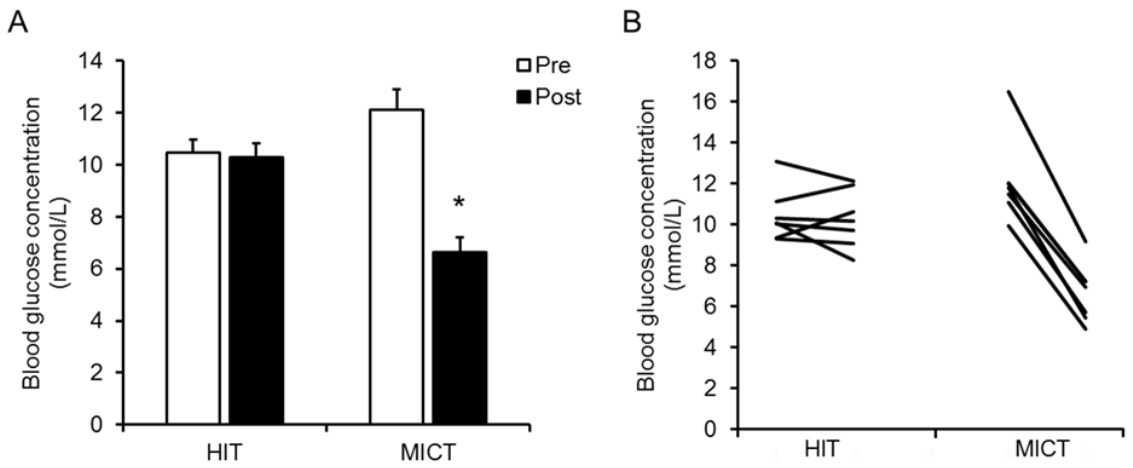

Figure 2 - Change in blood glucose following exercise in the fed state

Finger prick blood glucose concentrations were recorded immediately before and after exercise. As such, over the course of the six weeks of training we gathered pre and post exercise blood glucose concentrations from a total of 108 MICT training sessions and 87 HIT sessions in the fed state (86% and 69% of total possible sessions, respectively). Mean change in blood glucose concentration (A) and average change in blood glucose concentration during HIT and MICT over the 6 week training period (B). *Denotes a significant change from baseline (P<0.05).