

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

3

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

7

8 **SHORT TITLE:** HIT in people with type 1 diabetes

9

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30 **KEY WORDS**

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32 blood glucose; training intensity

33

34 **ABREVIATIONS**

35 HIT – High intensity interval training

36 MICT – Moderate intensity continuous training

37 CON – Control day of no exercise

38 aPWV – Aortic pulse wave velocity

39 CGMS – Continuous glucose monitoring system

40 CHO - Carbohydrate

41 SBP – Systolic blood pressure

42 DBP – Diastolic blood pressure

43 MAP – Mean arterial pressure

44 EXTOD – Exercising for type 1 diabetes

45 $\dot{V}O_{2max}$ – Aerobic capacity

46 W_{max} – Maximal power output

47 $\dot{V}O_{2peak}$ - Peak oxygen consumption

48 IMTG - Intramuscular triglyceride

49

50 **DISCLOSURE SUMMARY**

51 The authors have no conflicts of interest to disclose.

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57 **ABSTRACT**

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

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

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

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

81 INTRODUCTION

82 Regular exercise is recommended for people with type 1 diabetes to maintain overall
83 health and reduce the risk of macrovascular and microvascular complications, which
84 are a major cause of mortality and morbidity^{1,2}. The current guidelines for people
85 with type 1 diabetes are to undertake at least 150 minutes of moderate to vigorous
86 aerobic exercise per week, spread over at least three days per week, with no more
87 than two consecutive days without activity³. Benefits of exercise for those with type 1
88 diabetes include improved aerobic capacity ($\dot{V} O_{2max}$), insulin sensitivity, body
89 composition, endothelial function and blood lipid profile^{1,4-6}. Despite the benefits, few
90 people with type 1 diabetes achieve exercise targets and many programmes
91 designed to increase physical activity have failed^{7,8}. In addition to the barriers to
92 exercise cited by the general population, such as a perceived lack of time, work
93 commitments and cost⁹, people with type 1 diabetes face additional barriers
94 including fear of hypoglycaemia, loss of glycaemic control and inadequate
95 knowledge around exercise management^{10,11}.

96 To overcome a perceived lack of time, high intensity interval training (HIT) is
97 purported as a time-efficient alternative to moderate-intensity exercise to improve
98 numerous cardio-metabolic risk factors including $\dot{V} O_{2max}$, insulin sensitivity and
99 glycaemic control in people without type 1 diabetes^{12,13}. Furthermore, results from
100 our laboratory show that a single bout of HIT does not increase the risk of
101 hypoglycaemia in people with type 1 diabetes (Scott et al. unpublished observations,
102 see supplementary material¹⁴). Whether HIT offers a safe, effective and time-efficient
103 training strategy to improve cardio-metabolic health that reduces the risk of
104 hypoglycaemia in people with type 1 diabetes is yet to be investigated.

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

112

113 **RESEARCH DESIGN AND METHODS**

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

129

130 **Pre-training assessments**

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

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

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

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

165

166 **Exercise Training**

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

178

179 **Acute change in blood glucose with exercise**

180 Participants were able to attend their training session between 7am and 5pm
181 Monday to Friday. The amount and type of food was not controlled but we asked
182 participants not to fast before exercising and not to exercise within 30 minutes of a
183 meal with the aim being to study the effects of HIT and MICT under 'real world'
184 conditions. Therefore, these training sessions are defined as being in the 'fed' state
185 in this investigation. In line with advice that has been used in other studies¹⁷, and in
186 keeping with international agreed advice¹⁸, if patients were doing MICT within 2
187 hours of a meal they were asked to reduce their fast acting insulin at that meal by
188 50%. No adjustments were made if doing a HIT session. Before starting and after
189 completing each training session during the six-week training period, participant's
190 blood glucose concentrations were required to be between 7-14 mmol/L. If blood
191 glucose concentrations fell outside of this range corrective measures were taken;
192 glucose was ingested if blood glucose <7 mmol/L, and a light walk or insulin bolus
193 was advised if glucose >14 mmol/L, as well as checking blood ketones. In addition,
194 when they first started exercising they were asked to check their glucose at 2am and
195 to reduce their night time background insulin by 10%. Reduction of insulin at night
196 could be continued if the participant found that their glucose was going low overnight
197 on the day of exercise. All participants were asked to measure their blood glucose
198 before and after an exercise session, in addition participants in the MICT arm were
199 advised to check their blood glucose part-way through the exercise and to consume
200 carbohydrate as necessary to prevent hypoglycaemia. Over the course of the 6
201 weeks of training we gathered pre and post-exercise blood glucose concentrations
202 from a total of 108 (86%) MICT training sessions and 87 (69%) HIT sessions.

203

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·kg⁻¹·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 Monitoring²¹.
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

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

233

234 **RESULTS**

235 By design, there were no differences in age ($P=0.877$), $\dot{V}O_{2peak}$ ($P=0.371$) or duration
236 of type 1 diabetes ($P=0.291$) between the training groups at baseline. BMI was,
237 however, significantly higher in the HIT group compared to the MICT group
238 ($P=0.038$). Pre and post-training variables are presented in Table 1. Training
239 increased $\dot{V}O_{2peak}$ (HIT 14%, MICT 15%; $P<0.001$) and W_{max} (HIT 13%, MICT 14%;
240 $P<0.001$), with no difference between groups (Fig. 1). Six weeks of training also
241 improved aPWV ($P=0.001$) and there was no difference between groups. Systolic,
242 diastolic and mean arterial blood pressure did not improve following training
243 ($P=0.219$; $P=0.476$; $P=0.268$, respectively). There was no change in plasma
244 cholesterol or triglyceride concentrations with training ($P=0.881$; $P=0.652$,
245 respectively).

246

247 **Glycaemic control**

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

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

265

266 **Acute change in blood glucose during training sessions**

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

272

273 **DISCUSSION**

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

291 Aerobic capacity improved to a similar extent following six weeks of HIT and
292 MICT, despite the weekly time commitment being 54-90 minutes less for HIT than for
293 MICT. The 14% increase in $\dot{V}O_{2peak}$ observed in our investigation following HIT (a
294 mean increase of $4.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) is high in comparison to other studies using
295 similar protocols that tend to report changes of 7-10% in populations without type 1
296 diabetes²² and the only other study to examine the effect of sprint interval training in
297 people with type 1 diabetes (repeated 30-second maximal cycling bouts interspersed
298 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 mortality²⁰ and improvements
301 in $\dot{V}O_{2max}$ with exercise training are associated with a reduction in all-cause mortality
302 risk²⁴. In fact, Myers²⁰ found that there is a 8-17% reduction in all-cause mortality for
303 each 1-MET ($\sim 3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) 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 outcomes²⁷.

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 exist³⁰. 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

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

348 recorded when analysing CGMS data²¹. 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 guidelines³¹. 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 ($-4.43 \text{ mmol/L h}^{-1}$ on average) while the

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

374 The drop in blood glucose concentration during the MICT sessions is likely
375 due to the effects of short-acting insulin in the circulation. In healthy individuals,
376 blood glucose concentration remains stable during moderate-intensity aerobic
377 exercise because insulin secretion is suppressed progressively with exercise
378 duration and there is a gradual increase in glucagon and adrenaline resulting in
379 increased hepatic glucose production^{33,34}. Therefore, contraction-mediated glucose
380 uptake is matched by increased hepatic glucose production so that blood glucose
381 concentration remains stable at ~4.0-6.0 mmol/L³³. However, as insulin is supplied
382 exogenously in people with type 1 diabetes, hyperinsulinaemia is likely to occur
383 because of increased blood flow and mobilisation of insulin from its subcutaneous
384 depot, particularly if the injection site is in an exercised region³³. This results in
385 enhanced glucose uptake due to combined contraction-mediated and insulin-
386 stimulated GLUT4 translocation. The high insulin levels will also suppress the
387 exercise-mediated increases in glucagon and adrenaline and their ability to stimulate
388 hepatic glucose production³⁵. As a result, muscle glucose uptake during MICT will
389 exceed hepatic glucose production, leading to the large decreases in plasma
390 glucose concentration observed in this study (Fig. 2). Hyperinsulinaemia has also
391 been shown to suppress adipose tissue and intramuscular triglyceride (IMTG)
392 lipolysis in healthy individuals³⁶, which will reduce the contribution of lipids to the fuel
393 mixture oxidised during exercise. The combination of insulin and exercise-mediated
394 glucose disposal coupled with decreased hepatic glucose production and reduced
395 lipolysis and lipid oxidation increases the risk of hypoglycaemia during MICT. On the
396 other hand, the stable blood glucose concentrations following HIT are likely due to

397 greater plasma catecholamine (particularly noradrenaline) concentrations which lead
398 to an increase in hepatic glucose production, thus offsetting the effects of
399 hyperinsulinaemia³⁷. Previous research has shown that addition of a sprint to a bout
400 of moderate-intensity exercise in individuals with type 1 diabetes opposed the fall in
401 glycaemia during exercise and this was associated with a rise in catecholamines³⁸.
402 Following a bout of HIT, it may be speculated that the greater catecholamine
403 response compared to MICT may lead to stimulation of adipose tissue lipolysis and
404 increase oxidation of the released fatty acids in the muscle during recovery³⁹.

405 Another important observation, although not quantitatively reported here, was
406 the number of training sessions in which participants had to prevent or treat an
407 episode of hypoglycaemia by consuming fast-acting carbohydrate. During the MICT
408 sessions, participants were advised to stop exercising at least once to check their
409 blood glucose concentration in accordance with the EXTOD guidelines³¹, correct
410 accordingly with glucose if necessary, and then wait for their blood glucose to
411 stabilise before recommencing the training. Many of the participants in the MICT
412 condition found this frustrating and it would often mean that the already time
413 consuming 50-minute cycling sessions were even longer while blood glucose was
414 checked. The large drop in blood glucose concentration that we found during the
415 MICT sessions highlights why the guidelines recommend that carbohydrate should
416 be taken when doing more than 30 minutes of moderate-intensity exercise⁴⁰.
417 Therefore, these findings provide evidence that HIT may be a more practical form of
418 exercise for people with type 1 diabetes that regularly experience problems with
419 hypoglycaemia during exercise.

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

422 training, and 2) the monitoring of acute changes in blood glucose concentrations
423 during exercise throughout the intervention. We also acknowledge that there are
424 some limitations. The sample size of the study was small; however, the clear
425 significant increases in $\dot{V}O_{2peak}$ suggest that we have the power to conclude that HIT
426 is effective at improving $\dot{V}O_{2peak}$ in people with type 1 diabetes. Secondly, we did not
427 record insulin dose before and after the training intervention. This would be useful to
428 determine whether there is a change in insulin sensitivity as reduced insulin dosage
429 is associated with decreased risk of cardiovascular complications in people with type
430 1 diabetes^{41,42}.

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

437

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440 SNS is supported by PhD scholarship from Liverpool John Moores University.

441 **Registration**

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

444 **CONTRIBUTION STATEMENT**

445 SNS, MC, SOS, RCA, PN, DJC, TSP: conception and design of the experiments.
446 SNS, MC, SOS, RCA, PN: collection, analysis and interpretation of the data. SNS,
447 MC, SOS, RCA, PN, AJMW: drafting and revising the manuscript. All authors have
448 read and approved the final manuscript. SOS is the guarantor for the article. The
449 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·m ⁻²)	29.2 ± 1.2	29.2 ± 1.2	25.3 ± 1.2	25.2 ± 1.2
$\dot{V}O_{2peak}$ (ml·kg ⁻¹ ·min ⁻¹)	35.6 ± 2.6	40.5 ± 2.6*	32.1 ± 2.6	36.9 ± 3.2*
¹⁾ $\dot{V}O_{2peak}$ (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

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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 hypoglycaemia (%)	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
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Time in hyperglycaemia	33.3±16.7	63.0±16.3*	28.5±15.9	23.6±15.8
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(%)

Incidence of level 1	0.5±0.2	0.3±0.2	0.3±0.2	0.1±0.1
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hypoglycaemia

Incidence of level 2	0.0±0.0	0.2±0.2	0.3±0.2	0.0±0.0
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hypoglycaemia

Incidence of	0.5±0.2	0.8±0.2	0.5±0.2	0.3±0.2
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hyperglycaemia

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614 The 24h period was defined as 08:00-08:00h and nocturnal period as 24:00-06:00h.

615 Level 1 hypoglycaemia (≤ 3.9 mmol/L), level 2 (severe) hypoglycaemia (≤ 2.9 mmol/L),

616 target range (3.9-10 mmol/L) and hyperglycaemia (≥ 10 mmol/L). There were no

617 differences in any of the variables with training ($P > 0.05$).

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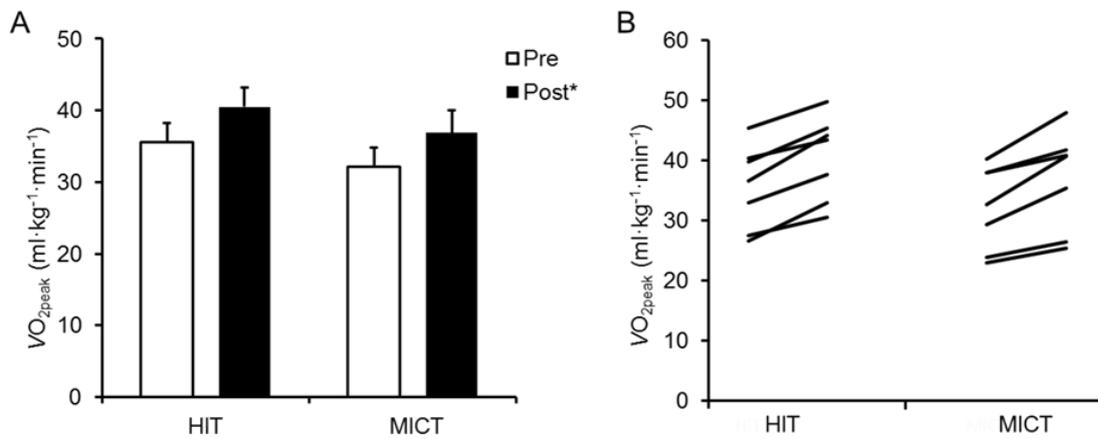
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629 **Figure 1** – Effect of six weeks of high intensity interval training (HIT) and moderate
630 intensity continuous training (MICT) on $\dot{V}O_{2peak}$.

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

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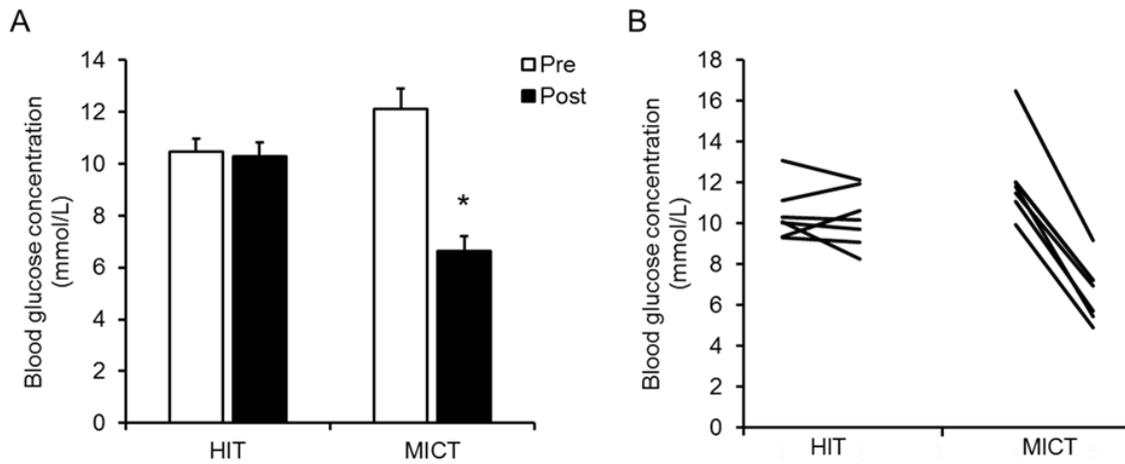
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640 **Figure 2** - Change in blood glucose following exercise in the fed state

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

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