

# Fasted high-intensity interval and moderate-intensity exercise do not lead to detrimental 24-hour blood glucose profiles

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DOI:  
[10.1210/jc.2018-01308](https://doi.org/10.1210/jc.2018-01308)

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Document Version  
Peer reviewed version

Citation for published version (Harvard):  
Scott, SN, Cocks, M, Andrews, RC, Narendran, P, Purewal, TS, Cuthbertson, DJ, Wagenmakers, AJM & Shepherd, SO 2018, 'Fasted high-intensity interval and moderate-intensity exercise do not lead to detrimental 24-hour blood glucose profiles', *The Journal of clinical endocrinology and metabolism*.  
<https://doi.org/10.1210/jc.2018-01308>

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Checked for eligibility: 10/10/2018

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**FULL TITLE:**

FASTED HIGH INTENSITY INTERVAL AND MODERATE INTENSITY CONTINUOUS EXERCISE ARE SAFE FOR PEOPLE WITH TYPE 1 DIABETES WITH NO DETRIMENTAL EFFECT ON 24-HOUR GLUCOSE LEVELS

**SHORT TITLE:**

Fasted exercise in people with type 1 diabetes

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Word count: 3079

Number of tables: 1

Number of figures: 3

## **ABSTRACT**

**OBJECTIVE** – To compare the effect of a bout of high intensity interval training (HIT) and a bout of moderate-intensity continuous training (MICT) on glucose levels over a 24-hour period.

**RESEARCH DESIGN AND METHODS** – Fourteen people with type 1 diabetes (duration of type 1 diabetes  $8.2 \pm 1.4$  years), all on basal-bolus regimen, completed a randomised counterbalanced crossover study. Continuous glucose monitoring was used to assess glycaemic control following a single bout of HIT (6 x 1min intervals) and 30mins of moderate-intensity continuous training (MICT) on separate days, compared to a non-exercise control day (CON). Exercise was undertaken following an overnight fast with omission of short-acting insulin. Finger-prick blood glucose samples were recorded pre and post-exercise to assess the acute changes in glycaemia during HIT and MICT.

**RESULTS** – There was no difference in the incidence of or % time spent in hypoglycaemia, hyperglycaemia or target range over the 24-hour and nocturnal period (24:00-06:00h) between CON, HIT and MICT ( $P>0.05$ ). Blood glucose concentrations were not significantly ( $P=0.49$ ) altered from pre to post-exercise with HIT ( $+0.39 \pm 0.42$  mmol/L) or MICT ( $-0.39 \pm 0.66$  mmol/L), with no difference between exercise modes ( $P=1.00$ ).

**CONCLUSIONS** – HIT or 30 minutes of MICT can be carried out after an overnight fast with no increased risk of hypoglycaemia or hyperglycaemia, and provided the starting glucose is between 7-14 mmol/L, no carbohydrate is needed for these exercises. As HIT is a time-efficient form of exercise, the efficacy and safety of long-term HIT should now be explored.

## **ABBREVIATIONS**

HIT – High intensity interval training

MICT – Moderate intensity continuous training

CON – Control day of no exercise

CGMS – Continuous glucose monitor system

CHO - Carbohydrate

EXTOD – Exercising for type 1 diabetes

## INTRODUCTION

Clinical guidelines recommend that people with type 1 diabetes perform at least 150 minutes of moderate-intensity physical activity per week (1). However, a single bout of moderate-intensity exercise in people with type 1 diabetes is associated with marked decreases in blood glucose concentration and increased risk of hypoglycaemia (2; 3). The potentially large drop in blood glucose during exercise and associated fear of acute and nocturnal hypoglycaemia means that many patients avoid exercise (4), putting them at increased risk of cardio-metabolic diseases. Clearly, safe and effective alternative forms of exercise that minimise the perceived barriers to exercise are needed for people with type 1 diabetes.

Lack of time has also been cited as an important barrier to exercise in people with type 1 diabetes (4). High intensity interval training (HIT), consisting of repeated bouts of high intensity exercise interspersed with low-intensity recovery, is purported as a time-efficient alternative to traditional moderate-intensity continuous training (MICT) in various groups without type 1 diabetes (5). Indeed, because the typical weekly training volume during a HIT programme is approximately one third of the time commitment required for MICT (6), HIT is able to minimise a perceived “lack of time” as a barrier to exercise. Importantly for people with type 1 diabetes, the addition of short bursts of high intensity exercise at regular intervals during a bout of MICT has been shown to assist in stabilising blood glucose concentration during exercise, and can prevent hypoglycaemia during and up to 2 hours post exercise (7; 8). It is proposed that the increase in catecholamines, growth hormone and cortisol during vigorous exercise ( $>80\% \dot{V}O_{2max}$ ) helps stabilise the glucose lowering effect of MICT (9). Therefore, in people with type 1 diabetes HIT may maintain blood glucose

concentrations and reduce the risk of hypoglycaemia both during exercise and overnight. To date, however, this has not been investigated.

The current investigation aimed to determine whether HIT maintained glucose in the normal range both during exercise and in the 24-hour period following exercise. To achieve this aim we examined the effects of a single bout of HIT and MICT following an overnight fast, compared to a control day with no exercise, on acute and 24-hour glucose concentrations in people with type 1 diabetes. Continuous glucose monitor data were analysed to assess 24-hour glycaemic control following exercise under controlled diet conditions using the most recent guidelines (10). Capillary blood sampling was used to assess change in blood glucose concentrations during the exercise bouts. We hypothesised that blood glucose concentrations would be maintained following HIT and that the incidence and time spent in hypoglycaemia would be lower, compared to MICT.

## **RESEARCH DESIGN AND METHODS**

Fourteen sedentary people with type 1 diabetes (6 men/8 women; age  $26 \pm 3$  years; BMI  $27.6 \pm 1.3$   $\text{kg}\cdot\text{m}^{-2}$ ;  $\dot{V}\text{O}_{2\text{peak}}$   $30.8 \pm 2.0$   $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; duration of type 1 diabetes  $8.2 \pm 1.4$  years) on a basal-bolus insulin regimen completed the study. Exclusion criteria were duration of type 1 diabetes  $<6$  months, insulin pump therapy, significant history of hyper or hypoglycaemia, obesity (BMI  $>32$   $\text{kg}\cdot\text{m}^{-2}$ ), 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-experimental procedures**

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). This information was used to determine appropriate workloads for subsequent exercise trials. 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.  $\dot{V}O_{2peak}$  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 their habitual caloric and macronutrient intake.

### **Study design and experimental protocol**

Participants completed a randomised counterbalanced crossover experiment, consisting of 3 intervention periods: control day with no exercise (CON), HIT and MICT (see Fig. 1 for protocol overview). Each intervention period lasted 24h during which the effect of a single session of exercise on subsequent 24h glycaemic control and risk of hypoglycaemia were assessed under standardised dietary, but otherwise

free living conditions. Periods were identical except for the exercise performed. Prior to the intervention periods participants had a Dexcom G4 Platinum CGMS (Dexcom, San Diego, CA, USA) inserted subcutaneously on the abdomen. Participants were trained on how to use the CGMS and instructed to calibrate the device a minimum of four times daily using capillary blood tests. Participants were not blinded to the CGMS meaning they could see their glucose values. 24h after the CGMS was inserted participants completed the control intervention. Participants did not attend the laboratory on the control day, but were provided with a standardised diet to consume while going about their normal daily activities.

The standardised diet was matched to each participant's habitual energy intake and consisted of three meals (breakfast, lunch and dinner; 50% CHO; 30% fat; 20% protein). Participants were instructed to consume these meals at pre-determined time-points throughout the day. Participants only consumed the food provided by the research team during this period. Additional snacks were only permitted to prevent hypoglycaemia. The diet was a 2-day rolling diet, matched for macronutrient and energy content between days, which ensured that participants consumed exactly the same food on the experimental days. Participants were also instructed to abstain from caffeine, alcohol and vigorous exercise. Participants completed a food diary to confirm that they had eaten the prescribed food at the correct times.

Following the control day participants completed the 2 exercise intervention periods in a randomised order separated by at least 48h. The exercise intervention periods were identical to the control intervention except participants attended the laboratory following an overnight fast and having omitted their short-acting insulin to perform a bout of either HIT or MICT. Following the exercise, participants left the



laboratory and returned to their normal daily activities. As on the control day participants were provided with a standardised diet to consume. This diet was identical to the control day and participants consumed each meal at the same pre-determined time-points throughout the day. Insulin dosage was not recorded.

### **Exercise Protocols**

Both exercise protocols were conducted on a stationary cycle ergometer (Excalibur Sport V2.0, Lode, Groningen, The Netherlands), and were preceded by a standardised 5 min warm-up at 50W. MICT consisted of 30 minutes continuous cycling at a workload equivalent to 65%  $\dot{V}O_{2peak}$ . HIT consisted of 6 x 1 minute intervals at a workload equivalent to 100%  $\dot{V}O_{2peak}$ , interspersed with 1 minute of rest. As such, the total time commitment of the HIT protocol (17 min) was ~half of that of the MICT protocol (35 min).

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

Blood glucose concentration was recorded before and after exercise through capillary fingertip sampling. This was to ensure that blood glucose levels were between 7-14 mmol/L, in accordance with the guidelines we developed in the Exercising for Type 1 Diabetes (EXTOD) study (11), meaning participants were safe to commence exercise and also safe to leave following exercise. If blood glucose was <7 mmol/L before exercise, glucose was ingested. If >14 mmol/L, a light walk or insulin was advised, as well as checking blood ketones (12).

## **Statistical analyses**

Continuous glucose monitor data were downloaded from the device using Dexcom Studio™ software (12.0.4.6). Data from the CGMS were analysed in accordance to the International Consensus on Use of Continuous Glucose monitoring guidelines (10). A one-way ANOVA with repeated measures was used to assess glycaemic control between the three conditions using the following metrics: percentage of time in level 1 hypoglycaemia ( $\leq 3.9$  mmol/L), level 2 hypoglycaemia ( $\leq 2.9$  mmol/L), time in target range (3.9-10 mmol/L) and hyperglycaemia ( $\geq 10$  mmol/L). Mean glucose and glycaemic variability using coefficient of variation were compared between conditions. Episodes of level 1 and 2 hypoglycaemia and hyperglycaemia were compared between conditions. The 24-hour period was defined as 08:00-08:00h and the nocturnal period was defined as 24:00-06:00h. A two factor repeated measures ANOVA was used to assess whether there was an acute change in blood glucose concentration following HIT and MICT in the fasted state with the within-subject factors 'training mode' and 'time point'. All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Data are presented as mean  $\pm$  SEM and significance was set at  $P \leq 0.05$ .

## **RESULTS**

### **24h glycaemic control**

Glucose data from the CGMS are presented in Table 1 and mean continuous glucose monitor traces over the 24-hour period in each condition are shown in Figure 2. The CGMS data revealed no differences in the time spent in level 1 hypoglycaemia ( $\leq 3.9$  mmol/L) over the 24-hour period ( $P=0.446$ ) or nocturnal period

( $P=0.944$ ) between the CON, HIT and MICT conditions. Similarly, there were no differences in the time spent in level 2 hypoglycaemia ( $\leq 2.9$  mmol/L) between the three conditions over the 24-hour period ( $P=0.518$ ) or nocturnal period ( $P=0.969$ ). There were also no differences in the time spent in target range or hyperglycaemia between the three conditions in the 24-hour or nocturnal periods ( $P>0.05$ ).

The incidence of level 1 hypoglycaemia over the 24-hour period ( $P=0.266$ ) and nocturnal period ( $P=0.522$ ) was no different between CON, HIT and MICT. There were no differences in the incidence of level 2 hypoglycaemia over the 24-hour ( $P=0.837$ ) or nocturnal ( $P=0.703$ ) period between conditions.

There was no report of different levels of snacking between the conditions during the CGMS period. Three participants arrived to the laboratory with a blood glucose of  $<7$  mmol/L on one trial so consumed  $\sim 200$ ml of Lucozade Sport Orange (20g CHO) and no participants arrived with a blood glucose  $>14$  mmol/L.

### **Acute change in blood glucose concentration**

Blood glucose concentrations did not drop during HIT ( $+0.39 \pm 0.42$  mmol/L) or MICT ( $-0.39 \pm 0.66$  mmol/L) undertaken in the fasted state ( $P=0.493$ ), with no difference between groups ( $P=1.00$ ; Fig. 3).

### **CONCLUSIONS**

This study examined the effects of a fasted bout of HIT and MICT on acute and 24-hour glucose levels in people with type 1 diabetes. The most important novel findings are that 1) there was no difference in the effect of HIT on 24-hour glucose compared to MICT, 2) both HIT and MICT performed following an overnight fast do not increase

the incidence or time spent in hypoglycaemia over the 24-hour or nocturnal period in comparison to a day of no exercise, and 3) blood glucose concentration remained stable during a bout of fasted HIT and MICT. This suggests that, a single bout of HIT or 30 minutes of MICT can be carried out after an overnight fast in people with type 1 diabetes with no increased risk of hypo or hyperglycaemia. In addition, provided the starting glucose is between 7-14 mmol/L, carbohydrate is not needed during these exercises in the fasted state.

The current exercise guidelines for people with type 1 diabetes report that aerobic exercise decreases blood glucose levels if performed during the postprandial period with insulin administration (1). This is supported by a systematic review and meta-analysis (3) that aggregated the results from 10 studies to estimate rate of change in glucose concentration in response to different types of exercise in people with type 1 diabetes. Garcia-Garcia et al. (3) reported that individuals typically experience a rapid decline in glycaemia during continuous exercise ( $-4.43 \text{ mmol/L h}^{-1}$  on average), whereas the response to intermittent high intensity exercise is more varied and dependent on the protocol. In contrast, our results showed that blood glucose concentration remained stable during both HIT and MICT, and the CGMS data showed no increased risk of hypoglycaemia over the 24-hour period. It is likely that our results do not agree with the findings of Garcia-Garcia et al. (3) because our study was performed in the morning following an overnight fast whereas their analysis did not control for time of day or nutritional status. Indeed, the most marked drop in blood glucose among the publications included in their meta-analysis was by Yamanouchi et al. (13) who reported a mean drop of 4.3 mmol/L following a 30 minute walk at  $<50\% \dot{V}O_{2\text{max}}$  after breakfast.

The same exercise guidelines by Colberg et al. (1) recommend that exercising while fasted may produce a lesser decrease or even a small increase in blood glucose concentration. The evidence to support this recommendation, however, is based on only one study that investigated the effects of fasted resistance training on glycaemia with no control day as a comparison (14). We now provide the first evidence that blood glucose concentrations are stable following both HIT and MICT when undertaken after an overnight fast. The findings of the current investigation should therefore be used to inform future exercise guidelines.

The use of CGMS allowed us to compare the complete 24-hour glucose profiles under dietary standardisation but otherwise free-living conditions to assess whether there is a delayed response in the risk of hypoglycaemia following HIT. Fear of hypoglycaemia during and after exercise, as well as during the nocturnal period, is a major barrier to exercise for people with type 1 diabetes, so it is essential to objectively establish whether exercise increases the risk. Here we found no differences in the time spent in level 1 ( $\leq 3.9$  mmol/L) or 2 ( $\leq 2.9$  mmol/L) hypoglycaemia in both the nocturnal period and 24-hour period following either HIT or MICT compared to a day of no exercise. The food diaries that participants completed indicated that they consumed the correct food and there was no difference in the amount of additional carbohydrate consumed to prevent hypoglycaemia between the conditions.

Based on our findings it appears that exercising following an overnight fast before using short-acting insulin helps to maintain blood glucose stability, irrespective of the mode or intensity of the exercise, which means that patients do not need to consume carbohydrate to avoid hypoglycaemia during exercise. However, the effects of longer duration MICT sessions will have to be tested. Future

research should investigate whether exercising regularly in the fasted state improves long-term glycaemic control. Indeed, Kennedy et al. (15) suggested that previous research may have failed to show glycaemic benefits of exercise because calorie intake and insulin dose around the time of exercise has not been controlled. Here, we studied our participants following an overnight fast to try to isolate the effect of exercise intensity alone, which is a strength of the study. Future research which examines how exercise of different type, intensities and duration carried out in the fasted state effects 24-hour glucose control are needed to help to produce more flexible exercise guidelines for people with type 1 diabetes.

This is the first study to investigate the effects of HIT on glycaemia in people with type 1 diabetes. The results suggest that HIT in the fasted state offers a time-efficient exercise mode that does not increase the risk of hypoglycaemia, thus, potentially overcoming two major barriers to exercise. As typical low-volume HIT protocols require 47-60% lower time commitment to MICT sessions, this may make HIT a more attractive training strategy to potentially increase exercise uptake and adherence in people with type 1 diabetes. The efficacy of long term HIT programmes will have to be explored in people with type 1 diabetes to determine whether this is an effective and time-efficient strategy to improve health. Furthermore, the effects of HIT in the non-fasted state have not been investigated.

The major strength of this investigation lies in the strict dietary standardisation during the CGMS period and the fact that the exercise sessions were performed at the same time of day, in the same nutritional state. Another strength is that by using CGMS we were able to study the individuals under free-living conditions, and thereby take an ecologically valid approach to investigate glucose levels following exercise. We also acknowledge that there are some limitations that will need to be

addressed with further research. Firstly, we did not record insulin dose during the CGMS period and participants were not blinded to the CGMS so they may have corrected their insulin dosage or taken carbohydrate to prevent lows if they felt it was necessary. The fact that there were no differences in food intake between the days lessens the chance that change in intake could be the cause. Secondly, the small sample size makes it difficult to draw conclusions that can be applied to the wider type 1 diabetes community. However, the sample size is in line with previous investigations that have compared the glycaemic effects of different exercise intensities in people with type 1 diabetes (16-18). There were three occasions where participants arrived to the laboratory with a blood glucose of  $<7$  mmol/L on one trial so needed to consume  $\sim 20$ g CHO before exercising for safety reasons. This highlights the difficulty of testing people with type 1 diabetes. However, excluding these participants from the statistical analyses made no difference to the results so their data were kept in the final analysis. Finally, the MICT was only 30 minutes in duration so we do not know the effects of prolonged ( $>30$  minutes) MICT sessions as this may lead to eventual falls in glycaemia and risk of hypoglycaemia. However, 30 minutes MICT sessions are in line with the current exercise recommendations of 30 minutes on 5 days of the week (1).

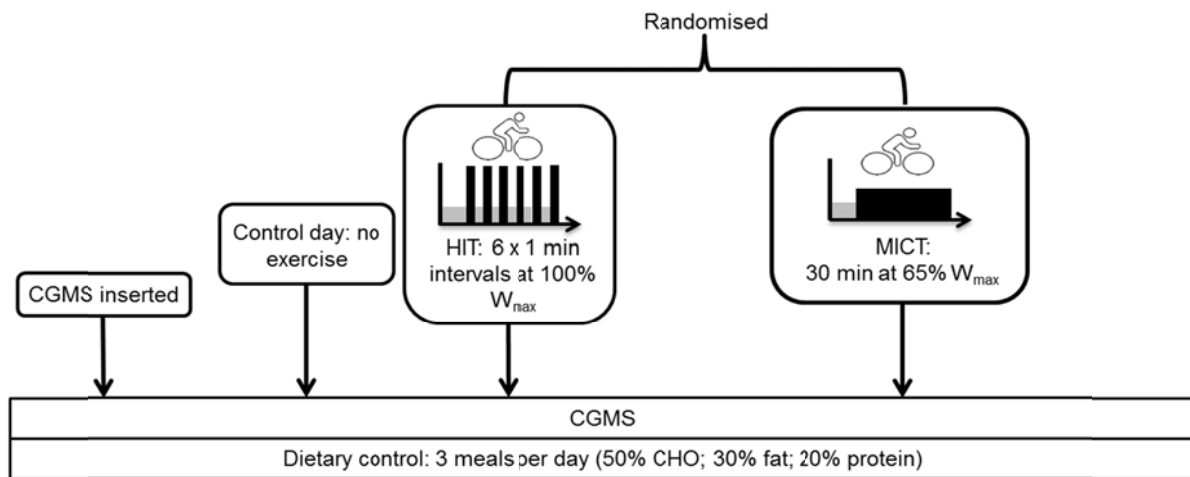
In conclusion, this is the first study to demonstrate that there is no increased risk of hypoglycaemia over the 24-hour period or nocturnal period following a single bout of HIT or 30 minutes of MICT in the fasted state, compared to a day of no exercise in individuals with type 1 diabetes. Secondly, blood glucose concentration is unchanged across HIT and MICT when undertaken following an overnight fast and having omitted short-acting insulin. Therefore, we recommend that in the fasted state, provided blood glucose starts between 7-14 mmol/L, carbohydrate is not needed for

HIT or a 30 minute MICT session. As HIT may offer a time-efficient and safe alternative for people with type 1 diabetes, future research should explore the efficacy of longer-term training programmes.

## **ACKNOWLEDGMENTS**

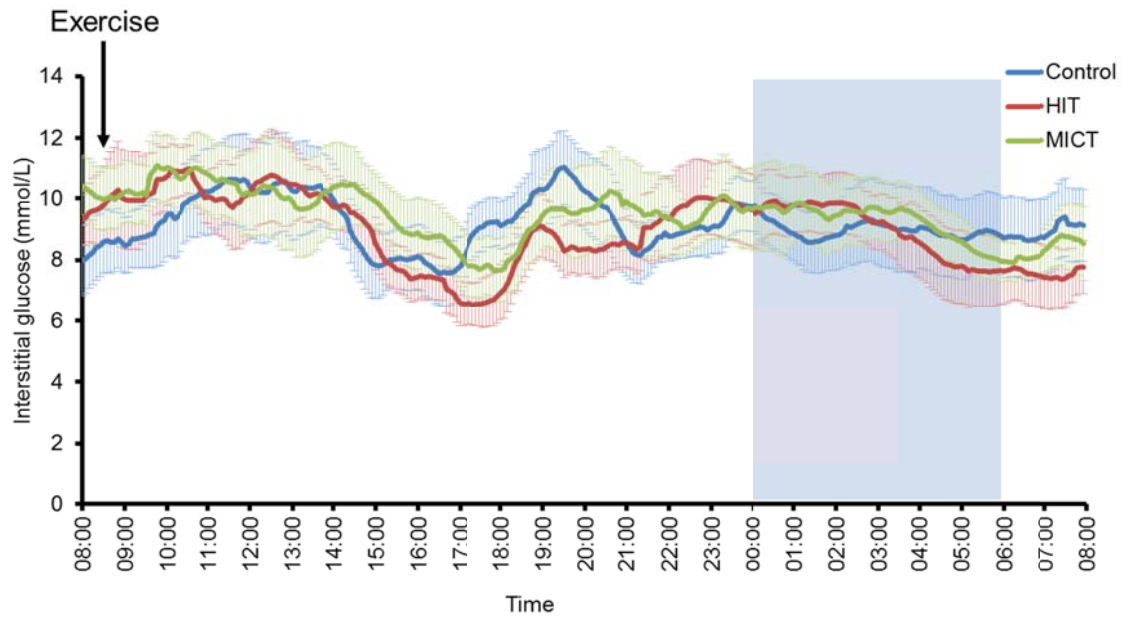
SNS, MC, SOS, RCA, PN, DJC, TSP: conception and design of the experiments. SNS, MC, SOS, RCA, PN: collection, analysis and interpretation of the data. SNS, MC, SOS, RCA, PN, AJMW: drafting and revising the manuscript. All authors have read and approved the final manuscript. SOS is the guarantor for the article. This work was supported by a grant from Diabetes Research & Wellness Foundation. SNS is supported by PhD scholarship from Liverpool John Moores University. The authors have no conflicts of interest to disclose.





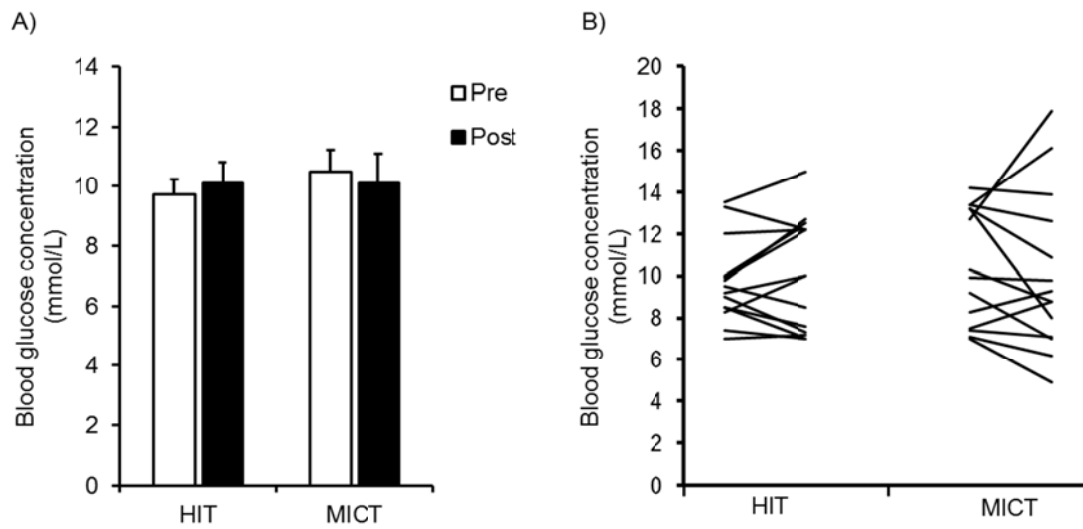
**Figure 1** - Study protocol

24h after the CGMS was inserted participants completed the control day. Participants did not attend the laboratory on the control day, but were provided with a standardised diet to consume while going about their normal daily activities. Following the control day, participants completed the two exercise intervention periods in a randomised order separated by at least 48h. The exercise intervention periods were identical to the control intervention except participants attended the laboratory following an overnight fast and having omitted their short-acting insulin to perform a bout of either high intensity interval training (HIT) or moderate intensity continuous training (MICT).



**Figure 2** – Continuous glucose monitor traces

Mean  $\pm$  SEM continuous glucose monitor traces over the 24-hour period (08:00-08:00h) on the day of no exercise (Control), HIT and MICT. The thick lines represent the mean of all the participants' glucose traces. Exercise was performed at approximately 8:30am. The shaded grey area represents the nocturnal period (24:00-06:00h).



**Figure 3** - Blood glucose concentrations during HIT and MICT

Mean ( $\pm$ S.E.M.) blood glucose concentrations pre and post exercise (A) and individual responses (B) to HIT and MICT sessions where the participants were overnight fasted and had omitted their fast-acting insulin.

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**Table 1** - Summary of continuous glucose monitor data

	CON	HIT	MICT
<b>24-hr period</b>			
Mean glucose (mmol/L)	9.2 ± 0.6	9.0 ± 0.4	9.5 ± 0.5
CV (%)	39 ± 2	39 ± 3	38 ± 3
Time in level 1 hypoglycaemia (%)	5.7 ± 1.4	7.5 ± 3.2	4.9 ± 2.0
Time in level 2 hypoglycaemia (%)	1.1 ± 0.5	3.1 ± 1.9	1.4 ± 0.7
Time in range (%)	60.5 ± 5.0	58.1 ± 3.6	59.3 ± 4.8
Time in hyperglycaemia (%)	33.7 ± 5.4	34.2 ± 3.6	35.8 ± 5.4
Incidence of level 1 hypoglycaemia	1.8 ± 0.4	2.2 ± 0.6	1.6 ± 0.5
Incidence of level 2 hypoglycaemia	0.6 ± 0.3	0.8 ± 0.4	0.6 ± 0.2
Incidence of hyperglycaemia	2.7 ± 0.3	3.1 ± 0.3	2.9 ± 0.3
<b>Nocturnal period</b>			
Mean glucose (mmol/L)	9.0 ± 1.0	9.0 ± 0.7	9.3 ± 0.9
CV (%)	25 ± 4	28 ± 5	19 ± 4
Time in level 1 hypoglycaemia (%)	8.9 ± 4.8	8.0 ± 3.6	7.9 ± 4.7
Time in level 2 hypoglycaemia (%)	1.5 ± 1.0	3.8 ± 2.4	4.0 ± 2.7
Time in range (%)	59.5 ± 9.7	56.8 ± 8.2	58.5 ± 8.8
Time in hyperglycaemia (%)	31.3 ± 10.2	35.1 ± 8.7	33.3 ± 9.8
Incidence of level 1 hypoglycaemia	0.4 ± 0.2	0.5 ± 0.3	0.4 ± 0.2
Incidence of level 2 hypoglycaemia	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Incidence of hyperglycaemia	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1

Summary of continuous glucose monitor data for the 24-hour period (08:00-08:00h) and nocturnal period (24:00-06:00h) for the control day with no exercise (CON) and the days on which HIT and MICT were performed. Level 1 hypoglycaemia ( $\leq 3.9$  mmol/L), level 2 (severe) hypoglycaemia ( $\leq 2.9$  mmol/L), target range (4-10 mmol/L) and hyperglycaemia ( $\geq 10$  mmol/L). Data are presented as mean  $\pm$  SEM. There were no differences in any of the factors between the conditions ( $P < 0.05$ ).

