



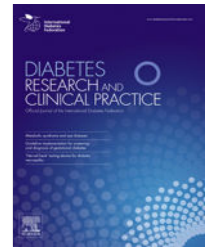
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Reproducibility in the cardiometabolic responses to high-intensity interval exercise in adults with type 1 diabetes



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ABSTRACT

Aims: Patients with type 1 diabetes (T1D) often report a rise in their blood glucose level following brief intense exercise. We sought to determine the reproducibility of the cardiometabolic responses to high-intensity interval training (HIIT).

Methods: Sixteen adults with T1D, using an optimized multiple daily injection with basal insulin glargine 300 U/mL (Gla-300), performed four fasted HIIT sessions over a 4–6-week period. Exercise consisted of high-intensity interval cycling and multimodal training over 25 min.

Results: Heart rate and rating of perceived exertion rose similarly in all sessions, as did lactate, catecholamine and growth hormone levels. Plasma glucose increased in response to HIIT in 62 of 64 visits (97%), with an overall increase of 3.7 ± 1.6 mmol/L (Mean \pm SD) ($P < 0.001$). In within-patient comparisons, the change in plasma glucose among the four HIIT sessions was significantly correlated with a composite correlation of 0.58 ($[r^2 = 0.34]$; 95% CI 0.35–0.80; $P < 0.01$).

Conclusions: Intersession observations of four separate HIIT sessions showed high intrasubject reproducibility in the cardiometabolic responses to exercise, including the rise in plasma glucose, when adults with T1D perform the activity in a fasted state.

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1. Introduction

Clinical counseling on exercise in type 1 diabetes (T1D) often focuses on the avoidance of hypoglycemia with insulin dose reductions and/or increased carbohydrate feeding. However, individuals with T1D can experience exercise-associated hyperglycemia, particularly when they perform activities that

are very intensive in nature, for a short duration (i.e. ≤ 20 min of active exercise time), such as intense cycling [1,2], a short sprint [3] or high-intensity interval training (HIIT) [4]. HIIT, now recommended for people living with type 1 or type 2 diabetes, for a variety of health and fitness reasons [5–7], refers to brief intervals of near-maximal effort, lasting from seconds to minutes, interspersed with periods of light activity [8]. The

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short duration and well established cardiometabolic benefits of HIIT [9] may make it a suitable exercise for individuals living with type 1 diabetes who may have limited training time [10]. Recent evidence suggests that HIIT is a time efficient training strategy that can improve aerobic capacity without promoting hypoglycemia in patients with type 1 diabetes [11].

While the reproducibility in the glycemic response to moderate-intensity continuous exercise in T1D has been established [12–15], the variability and reproducibility in the glycemic response to HIIT is unclear. This study aimed to definitively characterize the cardiometabolic responses to repeated sessions of HIIT, performed in a fasted state, in physically active individuals living with T1D. We hypothesized that there would be a significant degree of reproducibility within a patient's own cardiometabolic response to fasted HIIT.

2. Subjects, materials and methods

This study was a post hoc analysis of a primary investigation that examined the optimal bolus insulin correction factors for post-HIIT hyperglycemia [16]. It was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Council on Harmonisation Good Clinical Practice Guidelines. An independent ethics committee approved the protocol (#NCT03057470) and written informed consent was obtained from all study participants. In this sub-analysis of our previously published study [16], twelve males and four females with T1D, in good aerobic fitness ($VO_{2peak} = 40 \pm 6.6$ ml/kg/min) completed four identical fasted HIIT sessions, spaced at least 3 days apart, in our clinical research center. Subjects first completed an 8-week run-in period, using continuous glucose monitoring to optimize their multiple daily injection (MDI) regimens. All patients used insulin glargine 300 U/mL (Gla-300) (Toujeo™) as their basal insulin with stable dose throughout the study period. All participants had an initial exercise visit during run-in for the determination of peak aerobic capacity (VO_{2peak}). VO_{2peak} was determined from a 2-minute staged progressive cycling test to exhaustion on an electromagnetically braked cycle ergometer (ErgoSelect 100P/100 K; Ergoline, Windhagen, Germany) with continuous expired gas analysis (CardioCoach, Korr Medical Technologies Inc., Salt Lake City, Utah) and with continuous heart rate measurement (Polar Electro, Kempele, Finland). At the end of each incremental stage, the participant's rating of perceived exertion (Borg 6–20 scale) and heart rate were recorded. VO_{2peak} was considered to have been achieved if two of the following criteria occurred: (i) a leveling of oxygen consumption despite an increase in work rate; (ii) heart rate achieved age-predicted maximum ($220 - \text{age in years}$); (iii) volitional exhaustion despite verbal encouragement; and (iv) a respiratory exchange ratio of ≥ 1.10 . Peak work rate, as measured in watts, during the incremental cycling test was calculated from the last completed work stage.

Patients abstained from exercise 24 h prior to four identical in clinic HIIT sessions, with each session spaced at least 3 days apart. For each HIIT session, participants arrived at the clinical research center following an overnight fast with

their usual dose of Gla-300 administered the evening before. The lower and higher limit for pre-exercise (i.e. fasted) glucose concentration (i.e. ten minutes prior to the exercise start time) was set at 5.5 and 12.0 mmol/L, respectively, and the session was rescheduled if the pre-exercise glucose value was not in range for this type of intensive exercise. To help reduce potential confounders on the glycemic response to exercise, the session was also rescheduled if bolus insulin had been administered within 5 h because of hyperglycemia ($SMBG \geq 12$ mmol/L) or if hypoglycemia ($SMBG \leq 3.7$ mmol/L) occurred within an hour of exercise start time.

After the insertion of a venous catheter and baseline blood draws, individuals performed three 5-min bouts of high-intensity interval exercise, separated by two 5-min rest periods. Each HIIT session lasted 25 min in total and incorporated multiple muscle groups and exercise formats. The first 5-min bout of HIIT included a 30-sec cycling warm-up at 50% VO_{2peak} , followed by 30-sec bursts of cycling at 100-, 110-, 120-, 130- and 130% of the peak power output (Watts), as observed in the progressive VO_{2peak} cycling test, interspersed with 30 sec of active recovery cycling at a work rate corresponding to 50% VO_{2peak} . A 30-sec cycling cool down was then performed, followed by a 5-min rest break in a seated position for blood sample collection. The middle bout of activities within a HIIT session included a series of calisthenics: marching on the spot with dumbbells (~20 sec); jumping jacks (~20 sec); two burpees; two triceps push-ups; two burpees; two triceps push-ups (all together lasting ~20 sec); forearm plank (~20 sec); and medicine ball sweeps (~20 sec). This circuit was performed twice with a total active time of ~5 min. After a second 5-min rest period with blood collection, participants returned to the cycle ergometer to repeat a second 5-min HIIT cycling protocol (as described above). A 30-sec cycling cool down was then performed after which time the subject remained at rest seated in a chair for a 15-min recovery period. Throughout HIIT, a physiological monitoring system (Bioharness™) was used to continuously monitor heart rate, breathing frequency and accelerometry [17,18]. Heart rate was used to then characterize the intensity of the HIIT session by expressing it as a percent of maximal heart rate and by using the established heart rate to VO_2 relationship [19].

Plasma glucose and lactate levels were assessed at baseline, at each rest break, immediately after HIIT protocol and at 15 min in recovery from plasma isolated from non-arterialized blood drawn from an indwelling catheter (YSI 2300 STAT Plus, Yellow Springs, OH). Ratings of perceived exertion (Borg 6–20 scale) and heart rate (BioHarness 3.0, Zephyr Technology) were recorded at regular intervals throughout HIIT and heart rate was used to estimate relative oxygen consumption (i.e. % VO_{2peak}) during the active HIIT session, per the patient's established relationship between VO_2 and heart rate during the initial VO_{2peak} test. Serum insulin (Roche Diagnostics, catalog #: 12017547122) and growth hormone (Roche Diagnostics, catalog #: 05390125190) were measured by electrochemiluminescence immunoassay (Cobas e602 analyzer), while plasma free fatty acids were measured using a colorimetric method (Randox, Catalog Number: FA115) and catecholamines (i.e. epinephrine and norepinephrine) were measured using high performance liquid chromatography at baselines (–10 min, T-10), at the end

of HIIT (T25) and at 15 min in recovery (T40) by a central clinical laboratory (LifeLabs Medical Laboratories, Etobicoke, ON).

For each subject, the change in plasma glucose from baseline (T-10) to the end of the 15 min of recovery (T40) was calculated and the reproducibility was assessed by examining correlational analysis among the four study visits. Two-way repeated measures analysis of variance analysis was performed to compare the means of metabolic and physiologic variables measured over time in the four HIIT sessions. Simple and multiple linear regression models were performed to examine the associations between the change in glucose at T25 and T40 and lactate, epinephrine, and norepinephrine during HIIT. In all analyses, a P value < 0.05 was regarded as significant. Data are reported as mean \pm SD, unless otherwise stated.

3. Results

Sixteen participants completed four HIIT sessions in succession for a total of 64 visits (see Table 1 patient characteristics). The relative exercise intensity, as measured by %HR_{peak}, %VO_{2peak} and RPE across the four HIIT sessions is shown in Fig. 1. Across all sessions, RPE increased from 8.0 ± 3.6 to 19 ± 1.6 ($P < 0.001$); HR increased from 119 ± 15 bpm ($65 \pm 5.7\%$ of HR_{peak}) to 182 ± 13 bpm ($100 \pm 5\%$ of HR_{peak}) ($P < 0.001$) and relative VO₂ changed from 41 ± 12.5 to $94 \pm 10.6\%$ VO₂ peak ($P < 0.001$).

The pre-exercise (baseline) plasma glucose concentration was 8.8 ± 0.9 mmol/L, with an average within-patient coefficient of variation of $23 \pm 11\%$, for data collapsed across the four HIIT sessions. Plasma glucose levels rose significantly across all four sessions (main effect of time; $P < 0.001$), with values peaking at 15 min in recovery (T40) (Fig. 2A) (12.9 ± 2.7 ; 13.0 ± 2.9 ; 11.86 ± 2.8 ; 12.16 ± 2.5 mmol/L, for HIIT sessions 1–4, respectively, $P = 0.46$). The mean magnitude of the rise in glucose was similar across the four HIIT sessions (3.8 ± 1.7 ; 3.7 ± 1.7 ; 4.0 ± 2.4 ; 3.4 ± 1.9 mmol/L for HIIT sessions 1–4, respectively, $P = 0.57$) (Fig. 2B). For data collapsed across the four HIIT sessions, the mean increase was 3.7 ± 1.6 mmol/L (Fig. 2B). The change in plasma glucose was not associated with baseline glucose ($r^2 = 0.008$, NS) but was associated with the peak HR (in beats per minute) during the activity ($r^2 = 0.25$, $P < 0.001$).

A rise in plasma glucose occurred in 62 of 64 visits (97%) and post-HIIT hyperglycemia (plasma glucose ≥ 10 mmol/L

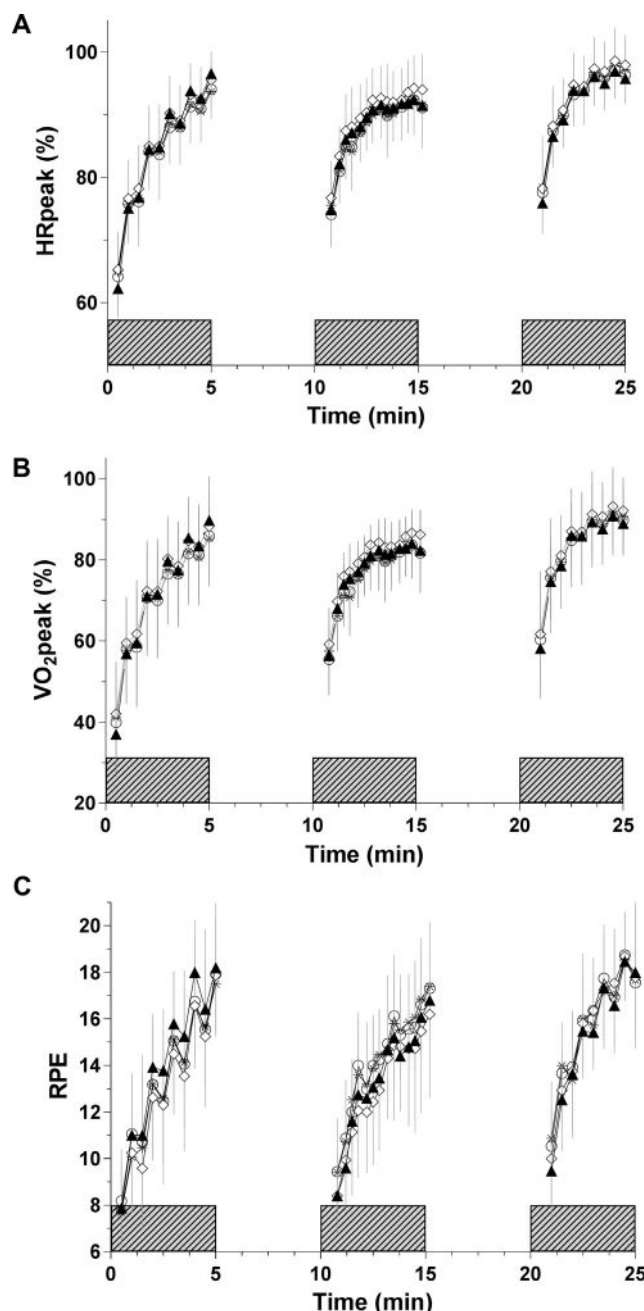


Fig. 1 – Percent peak heart rate (HR_{peak}), percent peak oxygen consumption (VO_{2peak}) and ratings of perceived exertion (RPE) across the four HIIT sessions. Each HIIT session consisted of five minutes of intermittent high-intensity cycling (left shaded boxes), five minutes of whole-body calisthenics (middle shaded boxes) and then a second 5-minute bout of intermittent high-intensity cycling (right shaded boxes) with two 5-minute breaks in between. Note: \blacktriangle = HIIT session 1; \diamond = HIIT session 2; \circ = HIIT session 3; \square = HIIT session 4.

Table 1 – Baseline characteristics of study participants.

N	16
Age (years)	34.7 \pm 10.3
Males, N (%)	12 (75)
Duration of T1D diagnosis (years)	17.3 \pm 11.3
HbA1c (mmol/mol)	54 \pm 9
HbA1c (%)	7.1 \pm 0.8
Body mass index (kg/m ²)	25.6 \pm 2.5
VO _{2peak} (ml/kg/min)	39.7 \pm 6.5
Basal insulin dose (U)	25.7 \pm 9.8
Data is presented as mean \pm standard deviation or as count (%). T1D = type 1 diabetes; VO ₂ = volume of oxygen.	

in a fasted state) occurred in 51 of 64 sessions (80%). The mean coefficient of variation for the change in plasma glucose in response to the four HIIT sessions across the 16 subjects was $33.9 \pm 39.3\%$. Table 2 shows the correlational change in plasma glucose from T-10 to T40 by HIIT session/

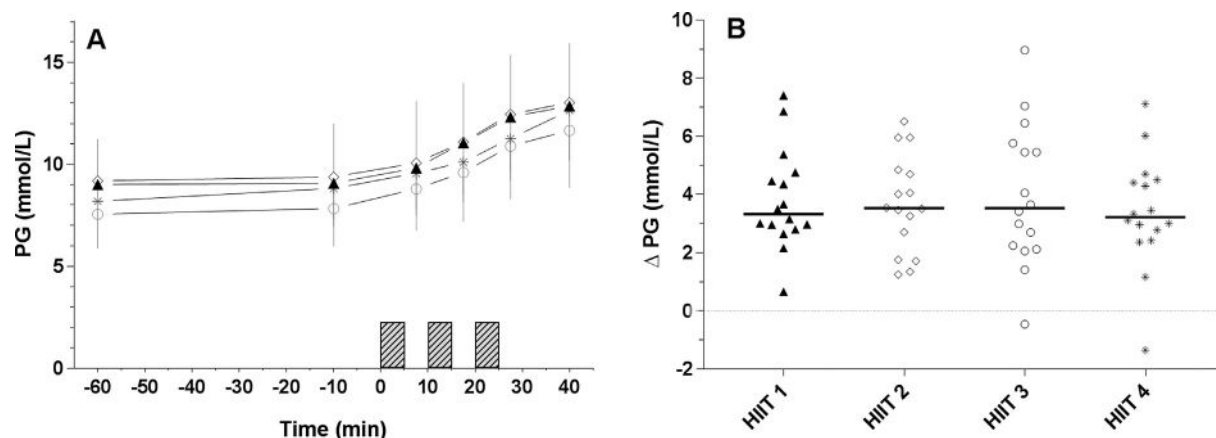


Fig. 2 – Effects of HIIT on plasma glucose (PG) concentration (panel A) and the change in plasma glucose concentration (Δ PG) during HIIT (panel B) across the four HIIT sessions. Note: \blacktriangle = HIIT session 1; \diamond = HIIT session 2; \circ = HIIT session 3; $*$ = HIIT session 4.

visit. The within-patient specific visit comparisons showed a range from the lowest correlation of 0.32 ($r^2 = 0.10$; 95% CI $-0.21, 0.70$) between visits 2 and 4 to the highest correlation of 0.84 ($r^2 = 0.71$; 95% CI $0.60-0.94$) between visits 3 and 4 (Table 2). The composite correlation for within-patient visit-to-visit comparisons, as measured by a repeated measures model, was 0.58 [$r^2 = 0.34$; 95% CI $0.35, 0.80$].

Plasma lactate, insulin, epinephrine, norepinephrine, growth hormone and insulin levels each rose significantly ($P < 0.001$) and the pattern of change was highly reproducible across all sessions (Fig. 3A–E). Free fatty acid levels dropped from $616 \pm 62 \mu\text{mol/L}$ at baseline to $435 \pm 14 \mu\text{mol/L}$ ($P < 0.05$) (Fig. 3F), while ketone levels also dropped significantly from $0.38 \pm 0.10 \text{ mmol/L}$ at baseline to $0.19 \pm 0.03 \text{ mmol/L}$ at T25 for data collapsed across the four HIIT sessions (Fig. 3F; $P < 0.05$). Lactate levels measured at T25 and T40 were significantly correlated with the rise in plasma glucose at T25 and T40 ($r^2 = 0.21, P = 0.0001$ and $r^2 = 0.12, P = 0.005$, respectively). Norepinephrine and epinephrine levels measured at T25 were correlated with the rise in plasma glucose at T25 ($r^2 = 0.08, P = 0.01$; $r^2 = 0.06, P = 0.06$, respectively) and at T40 ($r^2 = 0.14, P = 0.003$; $r^2 = 0.08, P = 0.02$, respectively). Norepinephrine, but not epinephrine, measured at T40 was correlated with

the rise in plasma glucose at T40. In multiple regression analyses, only lactate levels measured at T25 remained significantly associated with the change in plasma glucose at T25 ($r^2 = 0.22, P = 0.004$) and T40 ($r^2 = 0.20, P = 0.20$), after adjustment for norepinephrine and epinephrine.

4. Discussion

This study highlights that despite inter-individual differences, there is a high within-patient reproducibility in the plasma glucose response to multiple HIIT sessions, when performed in a fasted state, in individuals with T1D using MDI therapy. We show here that the magnitude of rise in plasma glucose in HIIT is associated with the individual's own rise in circulating lactate level during the activity. These findings extend our general appreciation of the reproducibility of the glycemic response to exercise which has already been established following prolonged steady state 'aerobic' exercise [12,13,15].

Our observation that fasted HIIT promotes a large and consistent increase in glucose concentration supports the notion that individualized strategies are needed to eliminate, or correct, the hyperglycemic response in individuals with T1D. It

Table 2 – Correlation of Change in Glucose (mmol/L) from T-10 to T40, by Visit.

Visit A	Visit B	N	Visit A change in glucose (mmol/L) mean \pm SD	Visit B change in glucose (mmol/L) mean \pm SD	Paired difference in change in glucose (mmol/L) mean \pm SD	Correlation (95% CI) ^a	R ²
Visit 1	Visit 2	16	3.8 \pm 1.7	3.7 \pm 1.7	-0.1 \pm 1.2	0.73 (0.37, 0.90)	0.53
	Visit 3	16	3.8 \pm 1.7	3.9 \pm 2.4	0.2 \pm 1.9	0.61 (0.16, 0.85)	0.37
	Visit 4	16	3.8 \pm 1.7	3.4 \pm 1.9	-0.4 \pm 1.8	0.53 (0.05, 0.81)	0.28
Visit 2	Visit 3	16	3.7 \pm 1.7	3.9 \pm 2.4	0.3 \pm 2.2	0.48 (-0.02, 0.79)	0.23
	Visit 4	16	3.7 \pm 1.7	3.4 \pm 1.9	-0.3 \pm 2.1	0.32 (-0.21, 0.70)	0.10
Visit 3	Visit 4	16	3.9 \pm 2.4	3.4 \pm 1.9	-0.6 \pm 1.3	0.84 (0.60, 0.94)	0.71
Composite		16	NA	NA	-0.2 \pm 1.8	0.58 (0.35, 0.80) ^b	0.34

^a Pearson correlation.

^b From a repeated measures model.

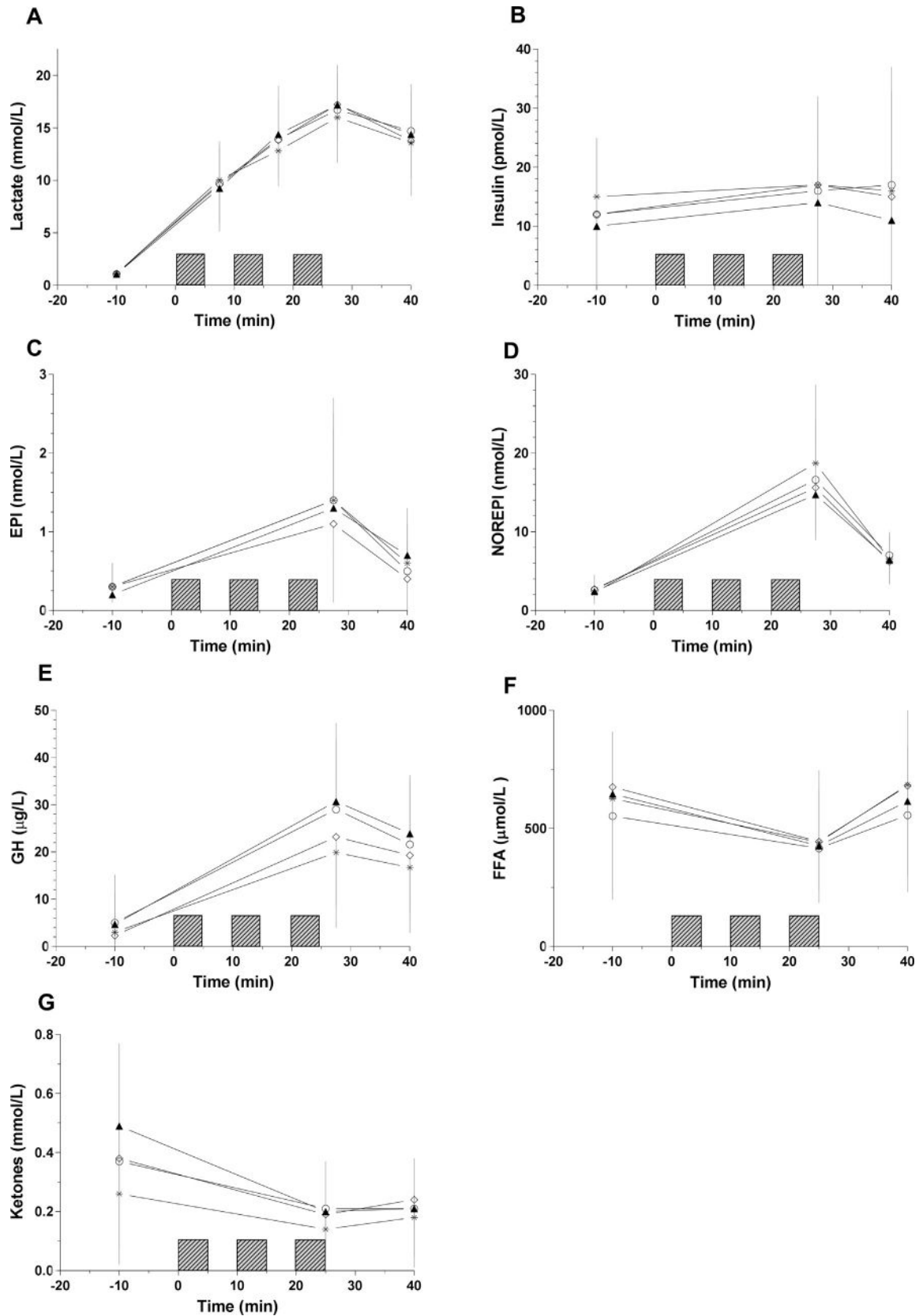


Fig. 3 – Plasma lactate (panel A), insulin (panel B), epinephrine (EPI) (panel C), norepinephrine (NOREPI) (panel D), growth hormone (GH) (panel E), free fatty acid (FFA) (panel F) and ketone levels (panel G) concentrations across the four HIIT sessions. Data are means ± SD. Note: ▲ = HIIT session 1; ◇ = HIIT session 2; ○ = HIIT session 3; * = HIIT session 4.

further has wide-ranging implications for the automated insulin delivery systems that are pre-programmed with higher glycemic targets, and thus less insulin delivery, to mitigate hypoglycemia risk for exercise [20–23].

We demonstrate that, in well-controlled T1D patients using MDI therapy that were in good aerobic fitness, a single 25-min session of HIIT performed in a fasted state consistently increases glucose concentration well above fasting targets (~4–7 mmol/L) and frequently induces hyperglycemia (fasting glucose > 10.0 mmol/L). A rise in plasma glucose in T1D in response to fasted cycling-based HIIT (four 30-sec maximal exercise bouts, each separated by a 4 min rest) has been reported previously [4], as has a rise in glucose in response to a brief bout of high-intensity cycling (i.e. at $\geq 80\%$ VO_2max for 10–15 min) [1,2]. However, not all forms of HIIT result in a clinically significant rise in glucose levels in patients with T1D, particularly if the exercise is performed in the afternoon, for more prolonged periods, or at a lower relative exercise intensity [24–27]. For example, a recent study by Scott and colleagues investigating a briefer and less intense form of fasted HIIT (6 \times 1 min interval cycling) in adults with T1D did not report a significant rise in glucose level [28]. We chose a mode of HIIT that included two 5-min bouts of intensive HIIT cycling and whole-body calisthenics. This type of HIIT most closely mimics what individuals with diabetes may perform in a real world circuit-based HIIT session, but it is not a traditional laboratory HIIT protocol [8]. The glycemic response observed with this type of HIIT appears to mimic what has been observed with high-intensity cycling to exhaustion [29] or with cycling-only HIIT performed in a fasted state [4]. Since HIIT does not always promote hyperglycemia in patients with T1D even when fasted [28], we suggest that insulin dosing decision-making should be made only after the confirmation of hyperglycemia post exercise.

Surprisingly, unlike lower intensity aerobic exercise [12,30], we did not observe a relationship between the pre-exercise plasma glucose concentration and the post-HIIT glucose rise. HIIT-associated hyperglycemia in the fasted state is thought to result from the rise in counterregulatory hormones that is unmatched by a physiological rise in insulin levels [25,29]. While several hormones may be driving the rise in glucose with HIIT (i.e. glucagon, cortisol, catecholamines and growth hormones), carefully controlled studies using glucose clamp techniques, glucose tracers, and somatostatin inhibition of endogenous glucagon secretion, with or without α - or β -receptor blockade, attribute the rise in glucose during vigorous exercise (i.e. >80% VO_2max) to the rise in catecholamines [2,31]. Although lactate itself can reduce skeletal muscle insulin signaling at rest, via reduced insulin receptor substrate 1/AKT phosphorylation [32], it is unlikely that lactate directly interferes with glucose uptake into exercising muscle where contraction-mediated glucose uptake dominates [33]. In fact, with gradual increase in exercise intensity, glucose uptake into skeletal muscle increases, along with the concomitant rise in lactate concentrations, at least until near maximal effort is achieved [34]. However, during short-term maximal dynamic exercise, glucose uptake into muscle is attenuated, as compared to submaximal exercise, likely through elevated intramuscular glucose 6-phosphate concentration, secondary to increased rates of muscle glycogenolysis

[35], a process that appears linked to the high adrenergic drive [33]. This attenuation in muscle glucose uptake at near maximal effort during HIIT coincides with a high rate of glucose production by the liver that remains elevated in early recovery [25].

Although this analysis was undertaken post hoc, a large number of sessions were compiled, in a controlled laboratory setting, in patients using an optimized MDI regimen and with a standardized basal insulin. It is important to emphasize, however, that we only assessed the metabolic response to fasted HIIT and only in those who were in good metabolic control on the morning of exercise. HIIT exercise performed at other times of day, when circulating insulin levels may be higher because of a recent insulin bolus, may not elicit a hyperglycemic effect [24,26,27,36]. Similarly, more prolonged HIIT sessions that incorporate some moderate-intensity activity may not be expected to produce hyperglycemia [24]. Future studies may consider assessment at other times of the day, more frequent exercise repetition (e.g., 2–3 times weekly), different HIIT protocols and additional variables that might impact glucose reproducibility (e.g., feeding, on-board bolus insulin, and stress).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.01.003>.

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