Optimal Insulin Correction Factor in Post–High-Intensity Exercise Hyperglycemia in Adults With Type 1 Diabetes: The FIT Study

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OBJECTIVE

Postexercise hyperglycemia, following high-intensity interval training (HIIT) in patients with type 1 diabetes (T1D), is largely underrecognized by the clinical community and generally undertreated. The aim of this study was to compare four multipliers of an individual's insulin correction factor (ICF) to treat post-HIIT hyperglycemia.

RESEARCH DESIGN AND METHODS

The FIT study had a randomized, crossover design in physically active subjects with T1D (mean ± SD age 34.9 ± 10.1 years, BMI 25.5 ± 2.5 kg/m^2, and HbA_{1c} 7.2 ± 0.9%) using multiple daily injections. Following an 8-week optimization period, with 300 units/mL insulin glargine used as the basal insulin, subjects performed four weekly sessions of 25 min of HIIT. If hyperglycemia (>8.0 mmol/L) resulted, subjects received a bolus insulin correction 15 min post-HIIT, based on their own ICF, adjusted by one of four multipliers: 0, 50, 100, or 150%.

RESULTS

Seventeen subjects completed 71 exercise trials, of which 64 (90%) resulted in hyperglycemia. At 40 min postexercise, plasma glucose (PG) increased from mean ± SD 8.8 ± 1.0 mmol/L at baseline to 12.7 ± 2.4 mmol/L (increase of 3.8 ± 1.5 mmol/L). After correction, adjusted mean ± SE PG was significantly reduced for the 50% (−2.3 ± 0.8 mmol/L, $P < 0.01$), 100% (−4.7 ± 0.8 mmol/L, $P < 0.001$), and 150% (−5.3 ± 0.8 mmol/L, $P < 0.001$) arms but had increased further in the 0% correction arm. Both the 100 and 150% corrections were more effective than the 50% correction ($P < 0.01$ and $P < 0.001$, respectively) but were not different from each other. Hypoglycemia was rare.

CONCLUSIONS

In post-HIIT hyperglycemia, correction based on a patient's usual ICF is safe and effective. Optimal PG reduction, with minimal hypoglycemia, occurred in the 100 and 150% correction arms.

Exercise is an important component of a healthy lifestyle for patients with type 1 diabetes (T1D), with documented benefits to glycemic control and insulin requirements, improved cardiovascular risk factors, and reduced risk of microvascular complications (1). However, exercise continues to present significant challenges to both patients and health care providers, since it can acutely cause hypoglycemia and

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hyperglycemia and can contribute to late hypoglycemia. Contributing factors include the content and timing of prior meals, and the timing of prior insulin dosing, but the type of exercise may be the single major determinant of the resulting glycemic excursion. Hypoglycemia is primarily associated with extended moderate-intensity aerobic exercise (walking, jogging, cycling, etc.) (2), while brief intense exercise (circuit training, sprinting, intense cycling/spinning, hockey, combat sports) has been reported to promote hyperglycemia, particularly in early recovery (3,4). High-intensity interval training (HIIT) has been growing in popularity in the past two decades and this year achieved the number one ranking for "most popular exercise trend" in the annual American College of Sports Medicine survey of >4,000 international registered exercise professionals (5). HIIT is especially favored by younger patients and may therefore present unique hyperglycemia challenges in otherwise healthy active patients living with T1D.

Hepatic glucose production during intense exercise exceeds the related transient increase in glucose disposal by skeletal muscle, thereby promoting hyperglycemia in both healthy subjects and subjects with diabetes (4). The hyperglycemic effect is more pronounced in subjects with diabetes who cannot naturally respond with an increase in insulin secretion (6). In patients with T1D, in a euglycemic insulin clamp setting, a doubling of insulin infusion rate after intense exercise partially offset postexercise hyperglycemia (7). Similarly, in a pilot study of resistance exercise in eight subjects with T1D, postexercise hyperglycemia was only partially corrected by a postexercise bolus insulin dose using 50% of each individual's insulin correction factor (ICF) (8). Insulin sensitivity may not actually be increased following high-intensity exercise; a higher insulin dose correction may actually be warranted. Trained men have been shown to have diminished oral glucose tolerance after intensive exercise (9), and in patients with T1D undergoing intense exercise, even a doubling of basal insulin infusion rate left patients with sustained hyperglycemia (10).

Several approaches have been established to prevent or treat exercise-related hypoglycemia, including reduction in insulin administration and/or increase in carbohydrate feeding (11,12). However, few clinical strategies have been investigated in the management of exercise-associated hyperglycemia. A common response to hyperglycemia is to administer a "corrective" dose of rapid-acting insulin analog based on an individual's ICF: the glucose concentration expected in response to each unit of rapid-acting insulin. However, most nonintense forms of exercise have been associated with increased insulin sensitivity, leading to the concern that this corrective approach to postexercise hyperglycemia may inadvertently increase the risk of late-onset hypoglycemia (13). Further, several forms of exercise have been linked to subsequent impairment of counterregulatory response in patients with T1D (13) such that overly aggressive insulin administration to correct postexercise hyperglycemia may lead to delayed or nocturnal hypoglycemia.

Currently, the postexercise hyperglycemia associated with HIIT has not been fully characterized, and its treatment remains an enigma. A recently published consensus statement on exercise management in T1D (7) provided only a brief mention of the hyperglycemia characteristic of HIIT exercise and only very limited guidance for the insulin therapy response. Clinical practice currently ranges from conservative observation to the commonly practiced "chasing the curve," involving repeated frequent doses of rapid-acting insulin until the hyperglycemia peak is resolved. The aim of this study was therefore to determine the glucose reducing effect of each of 50, 100, and 150% bolus insulin corrections, versus no correction, in patients with T1D, using each individual subject's ICF to address the postexercise hyperglycemia of HIIT.

RESEARCH DESIGN AND METHODS

The study was conducted in compliance with the ethics 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.

This study used a single-center, open-label, randomized, repeated-measures crossover design, evaluating four different multipliers of bolus ICFs, in physically active subjects with T1D using 300 units/mL insulin glargine (Gla-300) as their basal insulin.

Patients with T1D, using multiple daily injections (≥4 injections daily), and ≥30 units as total daily dose (TDD) for at least 6 months, were enrolled if they were between the ages of 18 and 55 years and had HbA_{1c} between 6.0 and 9.0% (42 and 75 mmol/mol) and a fasting C-peptide <0.7 ng/mL (0.23 nmol/L). Patients were excluded if they were following a very-low-calorie or other weight loss diet, had had one or more episodes of severe hypoglycemia during the past 6 months, had hypoglycemia unawareness, were pregnant or lactating, or had active diabetic retinopathy or unstable cardiovascular disease. Use of β-blockers or any noninsulin diabetes therapy was also excluded. Patients were then interviewed regarding frequency of regular physical activity and whether they exercised three or more times weekly for ≥30 min of moderate or vigorous aerobic activity per session, and patients underwent a screening assessment that included the determination of peak aerobic power, as measured on a cycle ergometer (VO_{2peak}), as previously described (14). Patients with VO_{2peak} ≥32 mL/kg/min (for females) or ≥35 mL/kg/min (for males) were enrolled and were entered into an 8-week run-in phase to convert their usual basal insulin to Gla-300 (Toujeo) administered at bedtime. Patients were monitored with continuous glucose monitoring (CGM) (Dexcom G4 Platinum System) for 2 weeks during the run-in period and were coached on dose optimization and carbohydrate counting to determine their individual insulin sensitivity, using the "rule of 100" (ICF = 100/TDD). The ICF chosen was monitored and adjusted over the course of the run-in period. Patients were then randomized to a sequence of four different bolus ICF multipliers: 0, 50, 100, and 150%.

Patients inserted a new CGM sensor 24–72 h before each exercise session, avoided exercise in the 24 h prior to exercise, and took their usual basal insulin dose the evening prior. On the morning of each exercise session, patients remained fasting except for water and were assessed for blood pressure, heart rate (HR), weight, waist circumference, and body fat percentage. Blood was collected for glucose, insulin,

catecholamines, ketones, growth hormone, lactate, and free fatty acids.

HIIT Session and Postexercise Insulin Treatments

Following a 5-min warm-up period, each subject performed three 5-min bouts of intense exercise at >80% of their peak HR, separated by 5-min rest periods, for a total span of 25 min. For the first and last 5-min bouts of HIIT, a cycle ergometer was used. Bouts included a 30-s warm-up (~50% VO_{2peak}) and five subsequent 30-s high-intensity phases (100, 110, 120, 130, and 130% of the peak power output achieved during the VO_{2peak} test) each separated by 30 s of light cycling at an intensity that elicited ~50% VO_{2peak}. The middle exercise bout used a rotation of typical HIIT-type exercises including spot marching with hand weights, jumping jacks, burpees, push-ups, forearm plank, and medicine ball sweep. Each exercise was undertaken for 20 s, and the circuit was repeated twice. HR, blood pressure, and capillary glucose were measured and blood was drawn in each rest period, with continuous monitoring of HR (Polar heart rate monitor), ventilation, and oxygen consumption (BioHarness 3.0; Zephyr Technology). Patients also provided frequent assessments of their ratings of perceived exertion (Borg 6–20 scale). Blood was drawn at baseline, 25 min, and 40 min for standard clinical-grade measurement of plasma insulin, ketone bodies, free fatty acids, catecholamines, and growth hormone (LifeLabs International Reference Laboratory, Toronto, Ontario, Canada). Venous blood was also collected at regular intervals (see below) throughout the study, and plasma was isolated and batch-assayed for glucose and lactate concentrations (Yellow Springs Instrument [YSI], Yellow Springs, OH).

If plasma glucose (PG) was >8.0 mmol/L at 15 min postexercise, an insulin dose was administered based on the following formula, where target glucose was set to 6.0 mmol/L and the ICF used was individualized:

$$Dose = \left[(PG - target\ glucose)/ICF\right] * randomized\ multiplier\ (i.e., 0, 50, 100, 150\%)$$

PG and lactate were measured every 15 min until a standardized meal was provided at 180 min postinsulin correction (0.75 g carbohydrate/kg body wt; Ensure Original Powder, Abbott Nutrition) (mixed with water) with an administration of a 25% reduction in usual bolus insulin according to the patient's own bolus calculator.

Patients were subsequently monitored for 21 h after exercise, during which they were provided an afternoon and an evening snack (with no bolus insulin to avoid contribution to delayed hypoglycemia) and a standardized dinner meal, using the patient's full bolus calculator dose. The patient's usual basal insulin dose was administered at 14 h postexercise, ~21 h following their last dose of basal insulin the prior night.

End Points

The primary end point was the reduction in PG at 3 h postexercise following a 0, 50, 100, and 150% bolus insulin correction (based on personal ICF). Secondary end points included the postprandial meal excursion after the first standardized meal and CGM parameters during the 3-h and the 21-h postexercise periods following the bolus insulin correction including: mean glucose; percentage of time in range (4.0–10.0 mmol/L), hypoglycemia (<4.0 mmol/L), and hyperglycemia (>10.0 mmol/L); and incidence of hypoglycemia.

Statistical Analysis

To determine a clinically significant reduction in PG of 0.5 mmol/L between the four insulin correction interventions, with an estimated SD of 1.5 mmol/L and a correlation between the glucose measurements of 0.5, we estimated that 15 subjects were needed in order to achieve a power of 0.8. Assuming 20% of subjects would not complete the study, we planned to enroll 18 subjects into the study.

Baseline characteristics are reported as mean ± SD for continuous variables and as counts (percentages) for categorical variables. The primary end point was analyzed with a mixed-effects model with repeated measures, with intervention as a fixed effect, subject as a random effect, and baseline glucose (pre-exercise glucose value) as a covariate. The secondary end points of percentage of time spent in hyperglycemia, euglycemia, and hypoglycemia were analyzed with mixed-effects models with repeated measures, with intervention as a fixed effect and subject as a random effect. All differences between interventions were tested with a two-sided α of 0.05, and all analyses were conducted with either SAS 9.4 (SAS, Cary, NC) or R, version 3.4 (www.r-project.org/about.html).

RESULTS

Of 25 patients screened for eligibility, 19 were randomized to a sequence of four identical weekly HIIT exercise sessions, with each followed by the application of investigational ICF multipliers (0, 50, 100, and 150%) to treat the resulting post-HIIT hyperglycemia. Two patients withdrew (owing to employment change and residency change, respectively), leaving 17 patients to be assessed for the primary end point (baseline characteristics in Table 1). Patients were otherwise included if they completed two or more of the HIIT sessions. A total of 71 exercise trials were completed: one session was aborted owing to hypoglycemia, and six sessions did not result in postexercise hyperglycemia (defined as PG >8.0 mmol/L at 15 min postexercise). Sixty-four of the 71 sessions (90%) resulted in postexercise hyperglycemia, were assigned the ICF multiplier for the insulin correction, and were included in the final analysis. Across all sessions, the pre-exercise mean ± SE PG at baseline was 8.8 ± 1.0 mmol/L. The mean PG increased to 12.0 ± 2.3 mmol/L after the 25-min HIIT session and reached 12.7 ± 2.4 mmol/L after a further 15-min rest period. The least squares mean difference in PG from baseline to 40 min was 3.8 ± 1.5 mmol/L.

At 40 min, individualized insulin correction boluses were given, subject to multiplier for the respective correction arm. The resulting mean bolus doses were as follows: 0%, 0 ± 0 units; 50%, 1.6 ± 0.7 units; 100%, 3.7 ± 1.4 units; and 150%, 4.3 ± 1.8 units.

At 180 min after the postexercise bolus insulin correction, adjusted mean ± SE PG was significantly reduced (Fig. 1) for the 50% (−2.3 ± 0.8 mmol/L, $P < 0.01$), 100% (−4.7 ± 0.8 mmol/L, $P < 0.001$), and 150% (−5.3 ± 0.8 mmol/L, $P < 0.001$) treatment arms but had increased further in the 0% correction arm (increase of 1.0 ± 0.8 mmol/L, not significant). Both the 100 and 150% corrections were more

Table 1—Baseline characteristics of FIT patients

	All screened patients	Final cohort (ITT)
N	25	17
Age (years)	33.4 ± 9.3	34.9 ± 10.1
Males	19 (76.0)	13 (76.5)
T1D duration (years)	17.1 ± 10.1	17.0 ± 11.0
Ethnicity		
Caucasian	20 (80)	13 (76.5)
Other	5 (20)	4 (23.5)
Smoking status		
Never	17 (68.0)	11 (64.7)
Former	7 (28.0)	5 (29.4)
Current	1 (4.0)	1 (5.9)
Weight (kg)	78.2 ± 15.0	77.9 ± 12.1
BMI (kg/m^2)	25.7 ± 3.2	25.5 ± 2.5
SBP (mmHg)	121.5 ± 15.1	119.1 ± 10.0
DBP (mmHg)	77.1 ± 9.2	75.2 ± 9.4
VO_{2peak} (mL/min/kg)	40.8 ± 6.3	40.3 ± 6.6
HbA_{1c} (%)	7.2 ± 0.9	7.2 ± 0.9
HbA_{1c} (mmol/mol)	55.0 ± 9.8	55.0 ± 9.8
eGFR (mL/min/1.73 m^2)	117.0 ± 13.0	117.2 ± 25.9
Basal insulin		
Insulin glargine U-100	17 (68.0)	13 (76.5)
Detemir	3 (12.)	1 (5.9)
NPH	1 (4.0)	1 (5.9)
Insulin glargine U-300	4 (16.0)	2 (11.8)
Bolus insulin		
Humalog	16 (64.0)	12 (70.6)
NovoRapid	8 (32.0)	4 (23.5)
Apidra	1 (4.0)	1 (5.9)
Insulin TDD (units)	49.8 ± 14.2	51.1 ± 14.7

Data are expressed as mean ± SD or as *N* (%) unless otherwise indicated. DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ITT, intention to treat; SBP, systolic blood pressure.

effective in reducing the 3-h follow-up PG than was the 50% correction ($P < 0.01$ and $P < 0.001$, respectively) but were not significantly different from each other.

Secondary End Points

At 3-h postinsulin correction, following the standardized meal provided, the 3-h postmeal PG excursions were typical, ranging from 1.8 ± 2.4 mmol/L in the 0% correction arm to 2.2 ± 3.3 mmol/L in the 150% correction arm, with no significant differences between arms.

Analysis of CGM data (Fig. 2 and Supplementary Table 1) showed that time in range was greatest for the 100% (37.3 ± 8.7%) and 150% (51.2 ± 7.4%) correction arms, both of which were greater than that for the 50% arm (28.7 ± 11.5%, not significant) and the 0% arm (10.4 ± 4.1% $P < 0.05$) over the initial 3 h following the insulin bolus. Time in hypoglycemia was minimal in all the correction arms but was highest in the 150% correction arm (4.4 ± 2.4%, $P < 0.05$ vs. the 50% correction arm).

In continual observation over the entire 21-h extended period (Fig. 2 and Supplementary Table 2), time in range was still highest in the 100% (42.7 ± 7.5%) and 150% (45.6 ± 7.8%) correction arms versus that in the 50% (30.9 ± 6.5%) and 0% (27.3 ± 7.1%) arms ($P < 0.05$). Time in hypoglycemia remained low in all groups and of the three correction arms, continued to be highest in the 150% correction arm (2.6 ± 4.1%, $P < 0.05$ vs. the 50% correction arm).

By the final 8 h of the observational period, which occurred overnight between 10:00 P.M. and 6:00 A.M., time in range had recovered in both the 50% arm (35.5 ± 26.0%) and the 0% correction arm (32.2 ± 38.1%) but had declined in the 100% arm (38.1 ± 41.2%) and the 150% arm (37.2 ± 38.9%), such that the four treatment arms were no longer significantly different (Supplementary Table 3).

Hypoglycemia events were rare during the 3-h period following the bolus insulin correction in all interventions (Table 2). In the full 21-h period following bolus correction, incidence of hypoglycemia remained low among all interventions but was more frequent in the 100 and 150% correction arms. When hypoglycemia did occur, it was more frequent during the daytime (21 events between 6:00 A.M. and 10:00 P.M.) compared with the overnight period (six events between 10:00 P.M. and 6:00 A.M.). Three events met criteria for clinically significant hypoglycemia (interstitial glucose <3.0 mmol/L), and these occurred in the 100 and 150% arms. There were no events of severe hypoglycemia.

There were no serious adverse events associated with HIIT or with insulin treatment in the exercise visits. Ketone levels

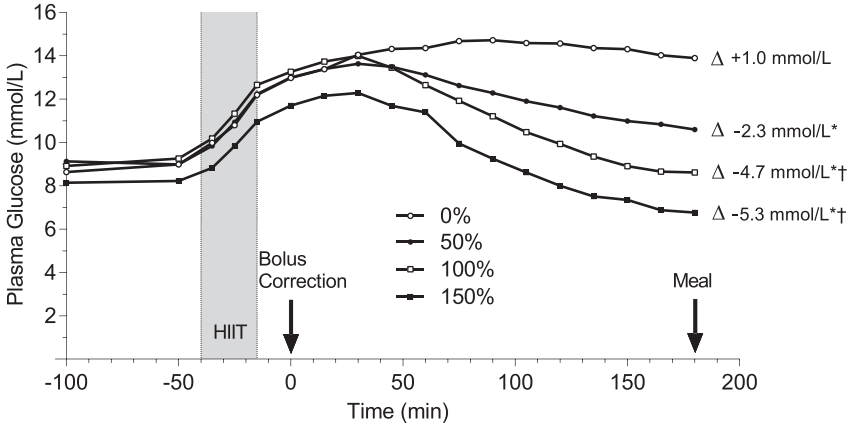

Figure 1—PG during exercise and 3-h postbolus insulin correction in the four interventions. *Significantly different compared with the 0% arm ($P < 0.05$); †significantly different compared with the 50% arm ($P < 0.05$).

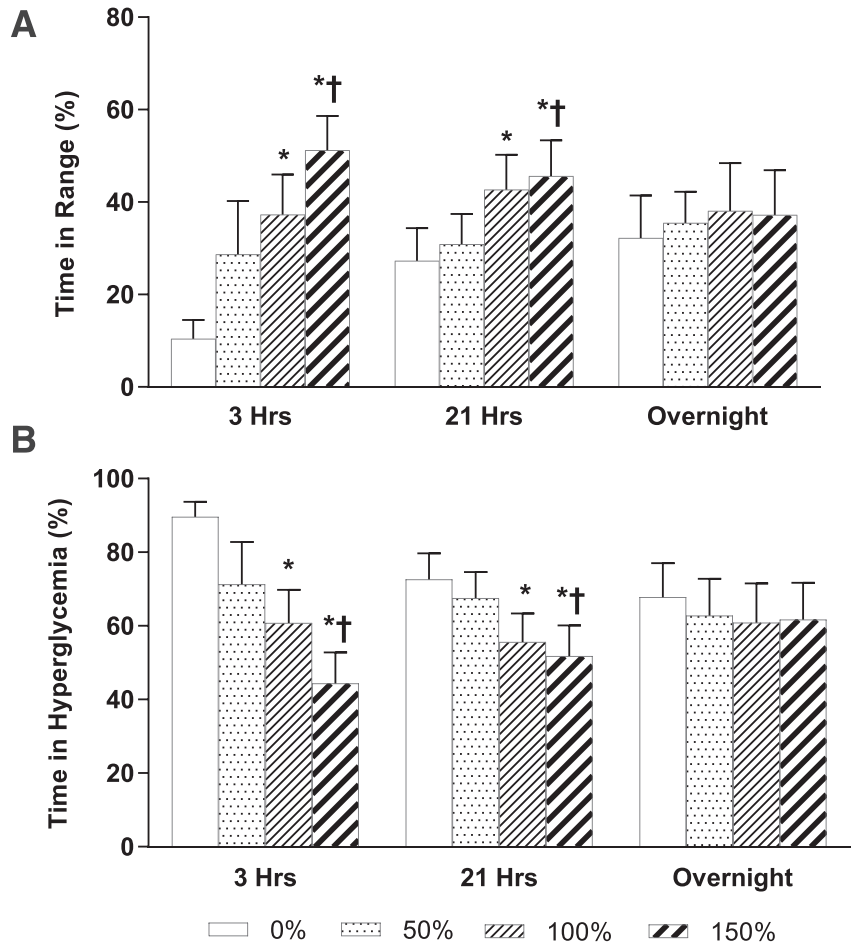

Figure 2—Percentage time spent in normoglycemia (*A*) and in hyperglycemia (*B*) following insulin correction. Data are presented as mean ± SE. *Significantly different compared with the 0% arm ($P < 0.05$); †significantly different compared with the 50% arm ($P < 0.05$). Hrs, hours.

were measured during exercise and declined slightly but significantly from 0.4 ± 0.5 mmol/L at baseline to 0.2 ± 0.2 mmol/L at 25 min and 0.2 ± 0.2 mmol/L at 40 min. Lactate levels rose significantly with exercise from 1.1 ± 0.3 mmol/L at baseline to 16.9 ± 3.7 mmol/L at 25 min and 14.3 ± 4.3 mmol/L at 40 min. There were no differences between the correction arms.

Insulin levels also rose slightly but significantly during and immediately after exercise from 13.4 ± 12.4 pmol/L at baseline to 16.4 ± 15.6 pmol/L at 25 min and 15.8 ± 17.8 pmol/L at 40 min. Catecholamine and growth hormone levels both rose with HIIT but did not differ between groups. Norepinephrine and growth hormone increased from baseline (2.5 ± 1.4 nmol/L and 3.6 ± 6.6 μg/L, respectively), peaked at the end of the 25-min exercise (16.3 ± 7.8 nmol/L and 25.3 ± 15.7 μg/L), and then decreased during the rest period to 6.3 ± 3.2 nmol/L and 19.4 ± 11.9 μg/L at 40 min after start of exercise. Epinephrine levels were 0.3 ± 0.2 nmol/L at baseline and increased at the end of the 25-min exercise (1.4 ± 1.2 nmol/L) and then decreased during the rest period to 0.6 ± 0.6 nmol/L.

Table 2—Incidence of total hypoglycemia, daytime hypoglycemia, and nighttime hypoglycemia following correction of postexercise hyperglycemia

Intervention arm	0%	50%	100%	150%
180 min following bolus correction				
Hypoglycemia (<4.0 mmol/L)	0	0	1	3
Clinically significant hypoglycemia (<3.0 mmol/L)	0	0	1	1
21 h following bolus correction				
Hypoglycemia (<4.0 mmol/L)	1	4	11	11
Daytime hypoglycemia (<4.0 mmol/L)	1	1	9	10
Nighttime hypoglycemia (<4.0 mmol/L)	0	3	2	1
Clinically significant hypoglycemia (<3.0 mmol/L)	0	0	1	2

CONCLUSIONS

HIIT is a popular form of exercise that has grown in prevalent use. Various expert groups have recently endorsed HIIT in their recommendations for people living with diabetes, including the American Diabetes Association position statement on physical activity and exercise and diabetes (15), a recent consensus statement (7), and Diabetes Canada's 2018 Clinical Practice Guidelines (16). Despite the growing awareness regarding the safety of HIIT in T1D, none of these statements have provided insulin- or carbohydrate-management guidance to control glycemia before or after HIIT. This study was the first to investigate several glycemic control options following HIIT for individuals living with T1D using multiple daily injections.

We found that, following a standardized 15-min HIIT exercise session in aerobically fit individuals with T1D, a significant degree of immediate postexercise hyperglycemia (mean increase of 3.8 ± 1.5 mmol/L) occurred consistently in 90% of sessions. Optimal approach to insulin therapy was tested using four different multipliers of the ICF of post-HIIT hyperglycemia. The 100 and 150% interventions resulted in a significantly greater improvement in PG 3-h post–insulin correction compared with 0% insulin correction. Both over 3 h and 21 h postcorrection, subjects in the 100 and 150% intervention arms spent significantly less time in hyperglycemia and more time in range compared with 0% arm. Time in hypoglycemia was rare and hypoglycemia events were very infrequent, both clinically using YSI analysis and subjective symptomatic scores and by CGM, although there were slightly more episodes of hypoglycemia in the 100 and 150% intervention arms compared with the 0 and 50% arms. With the results taken together, we suggest that an aggressive insulin correction (100–150%) can be performed postexer-

cise when documented hyperglycemia occurs.

Interestingly, the nocturnal period after HIIT, which represented the final 8 h of observation, showed similar glycemic control between all intervention arms. The effect of a bolus insulin correction for postexercise hyperglycemia may be limited to the immediate period following the correction and limited to the expected duration of the insulin correction (~3–6 h). It is possible that to effectively counter the postexercise hyperglycemic effect of HIIT, patients may actually require continued increases in insulin delivery, in the form of basal and/or bolus insulin treatment, over the subsequent 21-h period. However, care should be taken to monitor for increased risk for late-onset hypoglycemia.

High-intensity aerobic exercise activities, including HIIT, have been shown in prior investigation to be attributable to a typical, and possibly increased, degree of glucose production during the exercise, followed by a reduced level of glucose utilization, compared with moderate exercise (4,8). High-intensity exercise has similarly been associated with a marked increase in catecholamine production, which may restrict glucose uptake by skeletal muscle (17), a phenomenon that can be reproduced with catecholamine infusion without exercise (18). In subjects without diabetes, the resulting hyperglycemia leads to insulin release, accelerating glucose disposal; patients with T1D are unable to endogenously respond with insulin production, but exogenously infused insulin has also been shown to attenuate the postexercise hyperglycemia (19).

Interestingly, insulin levels did show a marginal increase during exercise in this study, likely representing redistribution from a subcutaneous depot of previously injected basal insulin. This finding has been observed with prolonged moderate-intensity aerobic exercise in individuals using continuous subcutaneous insulin infusion (19), even if basal insulin levels had been lowered in anticipation of exercise (20). The increased insulin levels did not prevent the expected postexercise hyperglycemia in this study but may contribute to exercise-associated hypoglycemia seen with moderate-intensity aerobic activity. Lactate levels also rose, likely reflecting the intensity of the exercise and its anaerobic component, although it is also possible that lactate contributes to insulin resistance, previously observed in rodent models (21). In patients with T1D, lactate elevations have been linked closely to post-HIIT hyperglycemia, and both have responded to exercise training (3) such that attenuation of post-HIIT hyperglycemia appears to be matched by attenuation of the plasma lactate increase postexercise.

Current guidelines recommend deferral of high-intensity exercise in settings of elevated ketone production (i.e., hypoinsulinemia, hyperglycemia) for fear that ketone levels may rise further (7). Our findings indicate that in HIIT, ketone levels do not rise and actually decline during and after HIIT exercise. In contrast, a recent study with closed-loop insulin therapy found that ketone levels were largely unchanged during continuous and HIIT types of exercise but increased significantly in early recovery, particularly after HIIT (22). The contrast with our study is surprising, given that their participants were studied in a fed and bolused state and exercised at a much lower intensity. Regardless, skeletal muscle under exercising conditions is known to be a net consumer of circulating ketone bodies even in patients with diabetes (23), possibly explaining the early decline in circulating ketones in this study.

Similar to findings in early investigations of high-intensity exercise (24), and more recent studies of resistance training (10) and of HIIT (3,4,22), we observed a clear and reproducible increase in glucose levels following HIIT that did not appear to diminish with repeated exposure. Not all studies investigating high-intensity exercise have confirmed this finding, and the inherent differences in study design are particularly hypothesis generating. For example, Guelfi et al. (25) found that addition of repeated 4-s sprints to continuous exercise caused only less glucose decline in a euglycemic clamp setting—not hyperglycemia. Tonoli et al. (26) and Moser et al. (27) similarly found a reduced risk of hypoglycemia, similarly using sprint-based exercises, in fed subjects, following a subcutaneous insulin bolus. Although interval sprinting has frequently been used, HIIT ideally involves a rotation between different exercises, thereby involving exertion of a number of muscle groups. The duration of the intervals may also differentiate our findings from very brief sprinting. Importantly, the pattern of hyperglycemic response appears to be consistent in subjects studied in a fasted and low insulin state. In contrast, studies of subjects after a carbohydrate load, whether intravenous (25) or oral (26,27), with prior insulin bolusing, have consistently shown modest hyperglycemia or only a limitation of hypoglycemia (22), suggesting that either the prior carbohydrate load or the prior insulin may have a fundamental role in determining the postexercise glycemic response. Finally, where high-intensity exercise has been studied as a hypoglycemia prevention tool within otherwise moderate-intensity exercise, the results are not directly comparable (14).

The study design has several strengths including crossover design to minimize the effect of individual variability in glycemic response, standardized use of the same basal insulin, an 8-week run-in phase to optimize insulin therapy and confirm an accurate individual ICF, supervision of the exercise sessions by one of three certified exercise physiologists, 21-h admission for observation, and the evaluation of four different ICF multipliers.

We also recognize several inherent limitations. As discussed, all exercise sessions were performed in the morning, in a fasted state, so the results may not be generalizable to exercise performed at other times or in a fed state. In addition, to avoid postexercise hypoglycemia, we chose to reduce the bolus insulin at the first meal by 25% and insulin was withheld for the afternoon and evening snacks. The resulting overnight trend toward hyperglycemia, which occurred even in the 100 and 150% arms, may be partially related to this insulin dose reduction at the meal following HIIT. Finally, these results have been found in the context of a randomized clinical trial where all of the exercise sessions were highly structured and supervised. Future studies should attempt to replicate these results in free-living individuals on other types of insulin-management regimens and further explore the possibility that exercise adaptations by skeletal muscle may influence the optimal individual ICF for management of post-HIIT hyperglycemia.

In summary, we have demonstrated here that HIIT in fasting patients with T1D produces a large and consistent hyperglycemic response immediately following exercise. We have also shown that insulin correction based on a patient's usual ICF, at either 100 or 150% of their ICF, is both safe and effective, especially for the 3-h period following exercise. Patient counseling and clinical practice guidelines should begin to more prominently distinguish between the hyperglycemia induced by HIIT and the classic concern of hypoglycemia associated with less intense forms of exercise. Patients and health care providers should be aware of the degree and duration of post-HIIT hyperglycemia and the potential benefit of an insulin correction bolus. Future investigation may explore whether an even longer duration of insulin correction, such as a temporary basal rate enhancement, may be additionally indicated to achieve a more durable return to normoglycemia following HIIT exercise.

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Author Contributions. R.A. wrote the manuscript. R.A. and M.C.R. designed the study. R.E.B. and A.L. analyzed data. R.E.B., A.L., and M.C.R. reviewed and provided critical edits to the manuscript. R.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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