A Randomized Crossover Trial Comparing Glucose Control During Moderate-Intensity, High-Intensity, and Resistance Exercise With Hybrid Closed-Loop Insulin Delivery While Profiling Potential Additional Signals in Adults With Type 1 Diabetes

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OBJECTIVE

To compare glucose control with hybrid closed-loop (HCL) when challenged by high intensity exercise (HIE), moderate intensity exercise (MIE), and resistance exercise (RE) while profiling counterregulatory hormones, lactate, ketones, and kinetic data in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This study was an open-label multisite randomized crossover trial. Adults with type 1 diabetes undertook 40 min of HIE, MIE, and RE in random order while using HCL (Medtronic MiniMed 670G) with a temporary target set 2 h prior to and during exercise and 15 g carbohydrates if pre-exercise glucose was <126 mg/dL to prevent hypoglycemia. Primary outcome was median (interquartile range) continuous glucose monitoring time-in-range (TIR; 70–180 mg/dL) for 14 h post–exercise commencement. Accelerometer data and venous glucose, ketones, lactate, and counterregulatory hormones were measured for 280 min post–exercise commencement.

RESULTS

Median TIR was 81% (67, 93%), 91% (80, 94%), and 80% (73, 89%) for 0–14 h post–exercise commencement for HIE, MIE, and RE, respectively (n = 30), with no difference between exercise types (MIE vs. HIE; P = 0.11, MIE vs. RE, P = 0.11; and HIE vs. RE, P = 0.90). Time-below-range was 0% for all exercise bouts. For HIE and RE compared with MIE, there were greater increases, respectively, in noradrenaline (P = 0.01 and P = 0.004), cortisol (P < 0.001 and P = 0.001), lactate ($P \leq 0.001$ and $P \leq 0.001$), and heart rate (P = 0.007 and P = 0.015). During HIE compared with MIE, there were greater increases in growth hormone (P = 0.024).

CONCLUSIONS

Under controlled conditions, HCL provided satisfactory glucose control with no difference between exercise type. Lactate, counterregulatory hormones, and kinetic data differentiate type and intensity of exercise, and their measurement may help inform insulin needs during exercise. However, their potential utility as modulators of insulin dosing will be limited by the pharmacokinetics of subcutaneous insulin delivery.

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Type 1 diabetes is characterized by an absence of β-cell function resulting in an absolute deficiency in the regulated release of insulin into the portal circulation. Hybrid closed-loop (HCL) systems represent a recent advance in the management of type 1 diabetes. They continuously adjust rapid-acting insulin delivery in response to interstitial glucose levels measured in real time to address basal requirements. Mealtime and exercise-related insulin dosing requires additional interventions by the user.

Exercise challenges HCL systems as insulin requirements change rapidly. Limitations imposed by the pharmacokinetics of subcutaneous insulin delivery mean that HCL systems cannot decrease plasma insulin concentrations accordingly (1–3). In addition, these devices do not receive input from those physiological signals which integrate glucose homeostatic mechanisms. Consequently, blood glucose levels tend to fall during moderate-intensity exercise (MIE) with a risk of hypoglycemia (4). In contrast, with high-intensity exercise (HIE), glucose and ketone levels may rise despite increased glucose utilization due to a robust counterregulatory hormone response (4–6). Furthermore, increased insulin sensitivity following exercise may persist for hours and may also vary with the type of exercise (7,8). Therefore, despite healthcare professional recommendations and health benefits associated with exercise, people with type 1 diabetes are often less active compared with their peers without type 1 diabetes (9–12). This may be due to concerns regarding hypoglycemia or a deterioration in their metabolic control (11,12).

To date, studies evaluating metabolic control with HCL during and after exercise in individuals with type 1 diabetes have largely focused on MIE, some with protocols not optimized for closed-loop functionality and using a variety of closed-loop platforms (13).

We hypothesized that glucose control with HCL during HIE, MIE, and resistance exercise (RE) would differ significantly and that the profiles of potential additional signals would be able to differentiate exercise type and intensity.

We therefore aimed to compare glucose control in adults with type 1 diabetes using a commercially available HCL system when challenged by HIE, MIE, and RE while profiling counterregulatory hormone responses, lactate, ketones, heart rate, and kinetic (accelerometry) data.

RESEARCH DESIGN AND METHODS

This was an open-label, randomized multistage crossover trial in adults with type 1 diabetes challenged with HIE, MIE, and RE interventions during HCL glucose control conducted at two sites (Melbourne, Victoria, Australia and Toronto, Ontario, Canada). The trial protocol was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee, and Advarra Institutional Review Board Services (Aurora, Ontario, Canada), and the trial was registered on the ANZCTR (www.anzctr.org.au, ACTRN12618000905268).

Participants

Inclusion criteria included 24–60 years of age; type 1 diabetes duration ≥1 year; (C-peptide <50 pmol/L); insulin pump therapy ≥6 months with established insulin delivery parameters and continuous glucose monitoring (CGM) experience; HbA_{1c} <9% (<75 mmol/mol); and able to complete the study protocol. Exclusion criteria included renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2); total daily insulin dose >150 units; untreated cardiovascular disease; severe hypoglycemia, diabetic ketoacidosis, or systemic steroid therapy within past 4 weeks; severe visual impairment; pregnancy; untreated thyroid, celiac or adrenal disease; any currently active major life-threatening illness; and any noninsulin medications that could alter blood glucose levels.

Study Design

Preliminary Testing

Baseline data were collected following informed consent, and participants were provided with, and educated in the use of, study devices. Peak cardiopulmonary oxygen consumption (VO_2peak) was assessed using a graded exercise test to volitional exhaustion on a cycle ergometer (Lode, Groningen, Netherlands). VO_2peak was determined using previously described criteria (14), maximum heart rate was defined as the highest heart rate achieved during the VO_2peak test, and the maximum power output (Wmax) achieved during the test was used to standardize exercise prescriptions for HIE and MIE. For RE prescription, strength testing was undertaken using guided completion of five exercises (two lower limb and three upper limb) with increasing weight load until the three-repetitions maximum was reached.

Exercise Testing

The exercise protocols included *1*) HIE: 40 min of HIE on an upright cycle ergometer, comprising 5 min at 25% Wmax, 4 × 4-min intervals at 80% of Wmax with 4-min rest between intervals, and 3-min cool down. *2*) MIE: 40 min of continuous MIE on an upright cycle ergometer, including 5-min warmup at 25% of Wmax, 32 min at 40% of Wmax, and 3-min cool down. This regimen is calculated as having the same metabolic equivalent minute energy expenditure as the continuous HIE regimen. *3*) RE: a whole-body strength-based session comprising of a circuit with five exercises (bicep curls, lunges, upright row, step-ups, and bench press) repeated for four sets. The first set was prescribed as 40% of the three-repetitions maximum, for eight repetitions, while the remaining three sets were prescribed as 80% of three-repetitions maximum, for eight repetitions, with all reps performed at an ∼2-s concentric, 2-s eccentric cadence.

Study Pump

All participants were trained in the use of the Medtronic MiniMed 670G. system (Medtronic, Northridge, CA) consisting of a glucose sensor (Enlite 3) and transmitter (GST3c MiniLink), coupled with an insulin pump incorporating a modified proportional-integral-derivative algorithm with insulin feedback (15,16). Target glucose was 120 mg/dL, with an optional increased temporary target of 150 mg/dL. Either insulin aspart or insulin lispro were used in the system. The study pumps were programmed with the participants' established insulin delivery settings, which were commenced in open-loop insulin delivery for at least 3 days. Participants had at least a 1-week run in with HCL prior to the in-clinic exercise sessions. A new sensor was inserted on the morning of the day prior to the exercise session, and HCL remained

activated until 6 days following exercise completion. Participants bolused for all meals using the pump's bolus calculator.

Experimental Design

Participants were assigned the three exercise protocols in random order, each separated by 1 to 4 weeks. Randomization was implemented by study investigators using a computerized sequence generation, and allocation was concealed via sequentially numbered sealed opaque envelopes until participant enrollment in the study had been completed.

On the day of the in-clinic exercise session, breakfast was consumed at home and insulin bolused according to usual practice. The final meal pre-exercise was a standardized lunch (45 g carbohydrate, 25 g protein, and 10 g fat) consumed at 1200 h, preceded by an insulin bolus as per the participant's bolus calculator. The participants arrived at the clinical trials center at ~1300 h. Accelerometers (Grey Innovation and FireFly 3D bespoke accelerometers) were worn on the wrist and ankle, a chest strap heart rate monitor was worn, and an intravenous cannula was inserted for blood sample collection. The closed-loop glucose set point was temporarily increased from 120 to 150 mg/dL 2 h prior to the allocated exercise regimen to align with recent recommendations for the use of HCL during exercise (13). Exercise commenced at 1600 h (i.e., 4 h after the standardized lunch). A 15-g carbohydrate snack was consumed prior to exercise if the plasma glucose was ≤126 mg/dL 10 min pre-exercise to help reduce hypoglycemia risk. The HCL set point was reverted to 120 mg/dL 10 min post-exercise.

Nonarterialized venous samples for measurement of glucose, lactate, ketones, free insulin, catecholamines, cortisol, growth hormone, and glucagon levels were collected at 30-min intervals commencing 60 min prior to exercise and then post–exercise commencement at 20-min intervals for 280 min. Following the last venous sample, participants consumed a standardized meal (55–60 g carbohydrate, 25–30 g protein, and 18–20 g fat) with an insulin bolus administered for the carbohydrate content only. Participants then departed the clinical trials center.

Plasma glucose and lactate concentrations were measured using a glucose analyzer (YSI 2300 STAT Plus Glucose Analyzer; YSI Life Sciences, Yellow Springs, OH). Blood ketones were measured using a ketone meter (FreeStyle Optium Neo; Abbott Diabetes Care, Alameda, CA). Plasma anti-insulin antibodies and free insulin concentrations were measured by radioimmunoassay as previously described (2). Norepinephrine was measured on heparinized plasma with a sodium metabisulfite additive by high-performance liquid chromatography on a Dionex Ultimate 3000 (Thermo Fisher Scientific, Waltham, MA). Glucagon concentration was measured on heparinized plasma collected with aprotinin by radioimmunoassay (Millipore, Billerica, MA). Serum cortisol level was measured by chemiluminescence (Thermo Fisher Scientific). Serum growth hormone concentration was measured by immunometric chemiluminescence with the IMMULITE 2000 Systems Analyzer (Siemens Healthcare Diagnostics, Sudbury, U.K.).

Outcomes

The primary outcome was CGM percent of time-in-range (TIR; 70–180 mg/dL) for the 14 h following exercise commencement with comparisons made between exercise protocols. Secondary CGM outcomes included standardized metrics (17,18), and sensor glucose-positive incremental area under the curve (AUC) 0–14 h after commencement of each exercise bout; for 280 min post–exercise commencement of each exercise bout; and the post-exercise overnight period (0000–0600 h). Other secondary outcomes included the change in plasma glucose, blood ketones, plasma insulin, counterregulatory hormones, accelerometry data and heart rate, from 1 h prior until 280 min post-exercise for each exercise bout. Safety outcomes were episodes of diabetic ketoacidosis and severe hypoglycemia (requiring assistance).

Statistical Analysis

Results are presented as median (interquartile range [IQR]) or frequency (percentage) unless otherwise specified, with significance at $P < 0.05$. We estimated that with a two-sided P of 0.05, a sample of $n = 30$ (assuming a 25% dropout rate) participating in each exercise modality would provide 80% power to detect a standardized mean difference of 0.6 in the primary end point. Pairwise comparison between exercise types for CGM outcomes was performed using Wilcoxon signed-rank test. Pearson correlation coefficient was calculated (within person) to evaluate the correlation among sensor glucose, insulin delivery, and free plasma insulin. Baseline hormone and heart rate levels were determined as mean of 60 min prior to exercise commencement. Incremental AUC for 280 min post-exercise commencement was calculated using trapezoidal rule. Peak hormone and heart rate levels were determined as the highest level within 280 min post–exercise commencement. All were compared among exercise types using Wilcoxon sign-rank test. Analyses were performed using Stata 16.1 (Stata Statistical Software Release 16; StataCorp LLC, College Station, TX).

RESULTS

Between 6 July 2018 and 10 December 2019, 17 men and 15 women were assessed for eligibility and qualified for inclusion. Two participants (one male and one female) withdrew prior to randomization (Supplementary Fig. 1). Thirty adults (16 men; aged [mean (SD)] 38 [9] years; HbA_{1c} 7.1% [1] [54 (11) mmol/mol]; duration of diabetes 23 [10] years; duration of insulin pump therapy 10 [5] years; total daily insulin 0.54 [0.20] units · kg^{-1} · day^{-1}; basal proportion of daily insulin 50% [11]; BMI 26 [3] kg · m^{-2}; max heart rate 177 [9] bpm; VO_2peak 38 [11] mL · kg^{-1} · min^{-1}; maximal power 244 [91] watts) completed the study between July 2018 and February 2020. Baseline characteristics are detailed in Supplementary Table 1. A total of 90 exercise sessions were successfully completed (30 HIE, 30 MIE, and 30 RE) by the 30 participants as detailed in Supplementary Table 2.

Glucose, Ketones, Lactate, and Insulin

For the primary end point, TIR (70–180 mg/dL) in the 14 h following exercise commencement (1600–0600 h), there were no differences for HIE, MIE, and RE (80.7% [66.7, 92.9%], 91.4% [79.8,

94.1%], and 80.1% [72.5, 89.3%], respectively). For the same time interval, time-below-range (<70 mg/dL) was <1% for all exercise interventions with a small, but statistically significant, increase in time-below-range for RE compared with MIE, and no differences observed between RE and HIE or MIE and HIE. There were no significant differences in all other CGM metrics or insulin delivery parameters between any exercise interventions (Table 1 and Supplementary Fig. 2).

During the 4 days prior to each exercise session, there were no episodes of severe hypoglycemia, and TIR was 72.2% (65.5, 80.7%) and time <70 mg/dL was 1.8% (0.8, 3.4%) (Supplementary Table 3). In the hour prior to exercise, 15 g of carbohydrate was administered to treat a plasma glucose of <70 mg/dL on 8 occasions out of 90 bouts of exercise (4 MIE, 3 HIE, and 1 RE). None required assistance. In the 15 min prior to exercise, in 19 additional sessions (7 MIE, 7 HIE, and 5 RE), participants were provided with 15 g supplemental carbohydrate for plasma glucose levels <126 mg/dL, as per protocol.

For the 280 min post–exercise commencement, TIR for HIE, MIE, and RE was >90%, while time-below-range was 0% for all exercise interventions with no differences observed. Time in tighter glucose range (70–140 mg/dL) (18) was significantly greater for MIE compared with RE by 30%, and mean sensor glucose was less for MIE compared with HIE by 20 mg/dL. Incremental AUC was greater for HIE and RE compared with MIE (Table 2). During the 280 min post–exercise commencement, seven sessions (one MIE, two HIE, and four RE) required 15 g carbohydrate to treat hypoglycemia. All participants had a blood glucose nadir >54 mg/dL in all sessions, except one participant undertaking RE with a nadir of 45 mg/dL.

Changes in plasma glucose, plasma free insulin, lactate, and ketone levels during the 280 min post–exercise commencement for the three exercise interventions are shown in Table 3, Fig. 1, and Supplementary Fig. 3. The percentage increment in lactate was more than fourfold greater in HIE and RE than for MIE. There were no significant differences observed for insulin delivery, plasma insulin, or ketones between exercise interventions. An analysis for the 120 min following exercise commencement showed a correlation between sensor glucose and insulin delivery (median within-person correlation of 0.63 [IQR 0.52, 0.79]), but no correlation between sensor glucose and free plasma insulin (median correlation of 0.18 [IQR 0.04, 0.41]) (Supplementary Fig. 4).

A post hoc analysis for the standardized meal following exercise revealed a TIR during the 4-h postmeal bolus of ~80% for all exercise interventions, with no differences observed. Time below range was 0% after the meal following all three exercise types. Postmeal, time in tighter glucose range was 15% greater with RE compared with MIE, and mean glucose concentration was highest following MIE. In addition, insulin delivery postmeal for MIE was significantly greater than RE, with the difference accounted for by automated basal insulin delivery (Table 2).

Overnight (1600–0600 h), there were no differences for TIR for HIE, MIE, and RE or time in hypoglycemia, which was 0% for all exercise interventions (Table 2).

Glucose Counterregulatory Hormones

Noradrenaline levels increased during all exercise interventions with a peak during exercise. The percentage increases from baseline following HIE and RE were approximately twice that of MIE with no differences between HIE and RE. Data for adrenaline and dopamine are not shown due to poor assay performance. Cortisol concentrations increased equally during HIE and RE, with the peak immediately post-exercise, both of which were more than fivefold greater than MIE. Growth hormone levels increased during all exercise interventions, with a peak occurring immediately post-exercise. The increase with HIE was significantly greater than with MIE. Other comparisons did not differ. Glucagon did not change with exercise (Table 3 and Fig. 1).

Heart Rate and Kinetic Data

There were no significant differences in the heart rate AUC between exercise conditions. However, the maximum increase in heart rate was greater in HIE and RE compared with MIE, with variation in heart rate reflecting the periodicity of each exercise intervention. Accelerometry data reflected the periodicity of the exercise and accelerometer placement. The ankle accelerometry data were similar between HIE and MIE, with significantly less acceleration detected in the RE. Greater variability in ankle acceleration was observed with HIE compared with MIE, which related to the interval nature of the exercise. The wrist accelerometry data identified greater acceleration in during RE compared with both MIE and HIE (Table 3 and Fig. 1).

Closed-Loop System Performance

Sensor mean absolute relative differences benchmarked against YSI for the 280 min post–exercise commencement were 7.4% (6.0, 10.3%), 6.4% (4.6, 8.9%), and 8.6% (5.9, 11.8%) for HIE, MIE, and RE, respectively. Percentage time in closed-loop for exercise was 100% for the duration of the study.

Adverse Events

There were no episodes of severe hypoglycemia or diabetic ketoacidosis.

CONCLUSIONS

This study is the first to evaluate the relative performance of an HCL system (MiniMed 670G system) when challenged by HIE, MIE, and RE in adults with type 1 diabetes while profiling lactate, plasma free insulin, glucose counterregulatory hormones, heart rate, and accelerometry data as potential additional signals. Glucose TIR was >80% and did not differ during the 14 h following the three exercise interventions. There were no episodes of severe hypoglycemia, and time-below-range (<70 mg/dL) was <1% across all exercise types. Importantly, time-below-range overnight after exercise was <1%, which is suggestive that the HCL system was effective in limiting post-exercise hypoglycemia. In addition, a comprehensive evaluation of TIR was undertaken over selected time blocks to evaluate specific challenges associated with the exercise interventions. Overall, our findings indicate that when international clinical guidelines are followed, HCL provided a consistent level of metabolic control across the spectrum of exercise, which met consensus targets (18). These guidelines include setting a higher glucose target 2 h prior to activity and commencing exercise with circulating glucose levels

Table 1—CGM outcomes and insulin delivery data for 0–14 h (1600–0600 h) post–exercise commencement

	HIE (0–14 h)	MIE (0–14 h)	RE (0–14 h)	*P* values
Glycemic outcomes				
Percent time 70–180 mg/dL (3.9–10 mmol/L)	80.7 (66.7, 92.9)	91.4 (79.8, 94.1)	80.1 (72.5, 89.3)	0.111 MIE vs. HIE, 0.109 MIE vs. RE, 0.902 HIE vs. RE
Percent time 70–140 mg/dL (3.9–7.8 mmol/L)	50.3 (40.5, 65.5)	56.6 (44.1, 67.1)	49.5 (43.1, 66.1)	0.416 MIE vs. HIE, 0.344 MIE vs. RE, 0.886 HIE vs. RE
Percent time <70 mg/dL (<3.9 mmol/L)	0.00 (0.00, 4.3)	0.00 (0.00, 1.2)	0.89 (0.00, 4.8)	0.737 MIE vs. HIE, 0.016 MIE vs. RE, 0.287 HIE vs. RE
Percent time <54 mg/dL (<3.0 mmol/L)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.415 MIE vs. HIE, 0.314 MIE vs. RE, 0.792 HIE vs. RE
Percent time >180 mg/dL (>10 mmol/L)	14.9 (5.4, 29.3)	8.6 (4.9, 20.2)	17.1 (7.1, 22.0)	0.237 MIE vs. HIE, 0.133 MIE vs. RE, 0.951 HIE vs. RE
Percent time >250 mg/dL (>13.9 mmol/L)	0.0 (0.0, 4.17)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.158 MIE vs. HIE, 0.560 MIE vs. RE, 0.664 HIE vs. RE
Mean glucose (mg/dL)	142.2 (129.6, 156.6)	135.0 (126.0, 149.4)	138.6 (127.8, 149.4)	0.206 MIE vs. HIE, 0.688 MIE vs. RE, 0.544 HIE vs. RE
Coefficient of variation (%)	24.4 (19.8, 33.8)	23.2 (19.8, 29.0)	26.4 (21.4, 31.5)	0.644 MIE vs. HIE, 0.530 MIE vs. RE, 0.178 HIE vs. RE
Insulin delivery				
Insulin: bolus (units)	8.1 (5.2, 11.5)	8.5 (6.2, 10.1)	8.4 (6.0, 10.9)	0.934 MIE vs. HIE, 0.918 MIE vs. RE, 0.600 HIE vs. RE
Insulin: basal (units)	11.8 (8.2, 15.6)	12.0 (7.6, 14.4)	12.1 (8.0, 15.3)	0.572 MIE vs. HIE, 0.813 MIE vs. RE, 0.644 HIE vs. RE
Insulin: total (units)	21.0 (14.7, 25.5)	19.5 (14.3, 25.6)	22.2 (14.8, 26.1)	0.975 MIE vs. HIE, 0.441 MIE vs. RE, 0.926 HIE vs. RE

Data are median (IQR) unless otherwise indicated.

in the upper half (126–180 mg/dL) of the target glucose range with no bolus insulin on board at exercise commencement (13,19–21).

A recent meta-analysis suggests that HCL systems may work more effectively than traditional continuous subcutaneous insulin infusion by increasing TIR during exercise (22). However, previous studies evaluating the performance of HCL systems with exercise have not comprehensively addressed the differential impact of HIE, MIE, and RE or profiled concomitant changes in glucose counterregulatory hormone levels, heart rate, and kinetic data (13). Usually, a single exercise intervention was implemented (most often MIE) and the HCL systems have not all been commercially available (13). In addition, glucose management protocols for exercise may not have been optimized for HCL functionality. Overall, the ∼80% TIR observed with this study compared favorably with that reported in prior publications using various commercial and experimental HCL systems, which range between 45 and 100% (4,23–27), and is markedly higher than the ∼60% TIR that is typically observed in this clinical population on exercise days with the current standard of care (28).

The assessment of postprandial glucose control with the post-exercise meal provides novel data. We observed a reduction in TIR after dinner by 15% for HIE, 18% for MIE, and 12.5% for RE predominantly due to hyperglycemia that persisted into the first half of the night. This occurred in a cohort with optimized glycemic control as evidenced by their baseline HbA_{1c} and their TIR in the days before exercise. Further research is warranted to optimize glycemia following the post-exercise meal. In addition, our data indicate that increases in insulin sensitivity, post-exercise, once the immediate impact of counterregulatory hormone responses has abated, may be greater with RE and HIE relative to MIE, as evidenced by lower mean sensor glucose in the postprandial period despite lower insulin delivery. Nevertheless, TIR for all types of exercise postprandially was still above the recommended target of >70% (18).

A secondary aim of this study was to profile additional biochemical and physical parameters as potential candidates for signaling the onset of and differentiating types of exercise. Our data extend the findings of Lee et al. (23) evaluating HIE and MIR that noradrenaline was among the first counterregulatory hormone to rise with a delayed response in cortisol and the magnitude of these responses reflect the intensity of the exercise. To this, we now contribute additional data regarding RE. Lactate's profile mirrored the catecholamine response, which, in conjunction with heart rate and body motion, differed according to the exercise intervention.

Nevertheless, changes in glucose levels following the modulation of insulin dosing by these potential additional signals would remain contingent upon the absorption characteristics of subcutaneous insulin. Our data confirm that changes in insulin delivery controlled by HCL mirrored sensor glucose during exercise. However, these changes were not reflected in plasma free insulin levels. Thus, the absence of a fall in glucose during HIE and RE was almost entirely attributable to the increase in counterregulatory hormone secretion (catecholamines, cortisol, and growth hormone) independent of HCL control. In contrast, during MIE, because of the less robust counterregulatory response (3), glucose levels fell markedly despite the reductions in insulin delivery. Therefore, any additional signals modulating insulin delivery at the time of, or

Table 2—CGM outcomes and insulin delivery data for 0–280 min post-exercise, postprandial (0–240 min after first meal post-exercise), and overnight 1600–0600 h glucose

	HIE (0–280 min)	MIE (0–280 min)	RE (0–280 min)	*P* values	HIE (postprandial)	MIE (postprandial)	RE (postprandial)	*P* values	HIE (overnight)	MIE (overnight)	RE (overnight)	*P* values
Percent time 70–180 mg/dL (%)	94.6 (76.8, 100.0)	98.2 (85.7, 100.0)	95.5 (65.5, 100.0)	0.558 HIE vs. MIE, 0.357 MIE vs. RE, 0.818 HIE vs. RE	79.2 (68.8, 100.0)	80.2 (60.4, 95.8)	82.3 (72.9, 100.0)	0.918 MIE vs. HIE, 0.636 MIE vs. RE, 0.711 HIE vs. RE	75.0 (54.2, 100.0)	96.5 (70.8, 100.0)	77.8 (62.5, 100.0)	0.119 MIE vs. HIE, 0.140 MIE vs. RE, 0.793 HIE vs. RE
Percent time 70–140 mg/dL (%)	52.7 (28.6, 80.4)	82.6 (58.9, 92.9)	52.7 (28.6, 82.1)	0.061 HIE vs. MIE, 0.037 MIE vs. RE, 0.887 HIE vs. RE	56.3 (37.5, 70.8)	39.6 (14.6, 68.8)	55.2 (39.6, 83.3)	0.084 MIE vs. HIE, 0.008 MIE vs. RE, 0.758 HIE vs. RE	58.3 (15.3, 75.0)	45.8 (18.2, 68.1)	37.5 (25.0, 69.4)	0.729 MIE vs. HIE, 0.837 MIE vs. RE, 0.724 HIE vs. RE
Percent time <70 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.156 HIE vs. MIE, 0.422 MIE vs. RE, 0.750 HIE vs. RE	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 14.6)	0.395 MIE vs. HIE, 0.019 MIE vs. RE, 0.151 HIE vs. RE	0.00 (0.00, 4.17)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.073 MIE vs. HIE, 0.433 MIE vs. RE, 0.275 HIE vs. RE
Percent time <54 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.500 HIE vs. MIE, 1.00 MIE vs. RE, 1.00 HIE vs. RE	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.083 MIE vs. HIE, 0.083 MIE vs. RE, 0.965 HIE vs. RE	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.655 MIE vs. HIE, 0.550 MIE vs. RE, 0.291 HIE vs. RE
Percent time >180 mg/dL (%)	0.90 (0.0, 23.2)	0.0 (0.0, 8.9)	1.8 (0.0, 32.1)	0.296 HIE vs. MIE, 0.246 MIE vs. RE, 0.906 HIE vs. RE	8.3 (0.0, 27.1)	19.8 (0.0, 39.6)	1.0 (0.0, 22.9)	0.409 MIE vs. HIE, 0.164 MIE vs. RE, 0.810 HIE vs. RE	1.4 (0.0, 45.8)	0.0 (0.0, 29.2)	22.2 (0.0, 37.5)	0.310 MIE vs. HIE, 0.210 MIE vs. RE, 0.297 HIE vs. RE
Percent time >250 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.500 HIE vs. MIE, 0.875 MIE vs. RE, 0.625 HIE vs. RE	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.906 MIE vs. HIE, 0.972 MIE vs. RE, 1.000 HIE vs. RE	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.622 MIE vs. HIE, 0.473 MIE vs. RE, 0.825 HIE vs. RE
Mean glucose (mg/dL)	140 (124.4, 159.7)	119.7 (111.8, 139)	135.7 (120.8, 154.6)	0.040 HIE vs. MIE, 0.164 MIE vs. RE, 0.499 HIE vs. RE	131.4 (111.6, 149.4)	149.4 (135, 169.2)	124.2 (99, 147.6)	0.045 MIE vs. HIE, 0.006 MIE vs. RE, 0.309 HIE vs. RE	135 (120.6, 172.8)	142.2 (122.4, 165.6)	147.6 (129.6, 160.2)	0.804 MIE vs. HIE, 0.336 MIE vs. RE, 0.339 HIE vs. RE
Coefficient of variation (%)	15.9 (11.4, 23.0)	16.4 (11.3, 21.6)	18.4 (13.6, 24.1)	0.777 HIE vs. MIE, 0.280 MIE vs. RE, 0.328 HIE vs. RE	23.2 (16.5, 32.2)	21.2 (13.8, 24.4)	22.6 (18.5, 29.5)	0.063 MIE vs. HIE, 0.107 MIE vs. RE, 0.837 HIE vs. RE	16.5 (11.8, 27.6)	16.0 (10.5, 18.9)	17.9 (12.2, 23.6)	0.315 MIE vs. HIE, 0.294 MIE vs. RE, 0.891 HIE vs. RE
AUC (mmol/L/h)	−2.5 (−119.5, 130.0)	−108.0 (−198.7, 34.0)	−1.7 (−91.4, 121.3)	0.026 HIE vs. MIE, 0.031 MIE vs. RE, 0.641 HIE vs. RE								
Insulin: bolus (units)	1.60 (0.30, 6.90)	1.30 (0.70, 2.72)	2.50 (1.20, 4.45)	0.75 HIE vs. MIE, 0.844 MIE vs. RE, 0.438 HIE vs.RE	7.30 (5.05, 9.50)	7.37 (5.30, 9.50)	7.20 (5.25, 8.90)	0.411 HIE vs. MIE, 0.789 MIE vs. RE, 0.703 HIE vs. RE	0.00 (0.00, 0.60)	0.00 (0.00, 1.15)	0.00 (0.00, 1.20)	0.411 HIE vs. MIE, 0.789 MIE vs. RE, 0.703 HIE vs. RE
Insulin: basal (units)	4.70 (3.43, 6.87)	3.95 (3.05, 6.75)	4.31 (3.33, 7.20)	0.262 HIE vs. MIE, 0.452 MIE vs. RE, 0.761 HIE vs. RE	1.58 (1.00, 3.13)	2.19 (1.24, 3.72)	1.70 (0.80, 3.30)	0.044 HIE vs. MIE, 0.127 MIE vs. RE, 0.374 HIE vs. RE	5.25 (3.55, 7.07)	5.00 (3.40, 7.50)	6.13 (3.28, 8.10)	0.044 HIE vs. MIE, 0.127 MIE vs. RE, 0.374 HIE vs. RE
Insulin: total (units)	4.96 (3.43, 8.07)	4.55 (3.12, 6.90)	4.93 (3.33, 7.70)	0.245 HIE vs. MIE, 0.247 MIE vs. RE, 0.939 HIE vs. RE	9.52 (6.62, 11.27)	9.70 (7.12, 12.47)	9.59 (6.30, 11.50)	0.572 HIE vs. MIE, 0.032 MIE vs. RE, 0.797 HIE vs. RE	5.65 (3.55, 7.45)	5.85 (3.49, 9.05)	6.58 (3.78, 8.57)	0.572 HIE vs. MIE, 0.032 MIE vs. RE, 0.797 HIE vs. RE

Data are median (IQR) unless otherwise indicated. Incremental AUC from baseline.

Table 3—Changes in counterregulatory hormones, heart rate, lactate, ketones, and plasma insulin with MIE, HIE, and RE

	MIE AUC (min · x*)	HIE AUC (min · x*)	RE AUC (min · x*)	*P* value	MIE time to peak (min)	HIE time to peak (min)	RE time to peak (min)	*P* value	MIE increase (%)	HIE increase (%)	RE increase (%)	*P* value
Glucagon (pg/mL)	186 (26, 503)	238 (22, 610)	206 (0, 407)	0.792 HIE vs. MIE, 0.509 MIE vs. RE, 0.289 HIE vs. RE	60.0 (40.0, 180.0)	70.0 (40.0, 100.0)	70.0 (40.0, 280.0)	0.577 HIE vs. MIE, 0.875 MIE vs. RE, 0.681 HIE vs. RE	9.0 (3.1, 20.9)	11.6 (1.6, 23.1)	12.1 (0.0, 16.3)	0.968 HIE vs. MIE, 0.692 MIE vs. RE, 0.338 HIE vs. RE
Noradrenaline (pmol/L)	117,219 (62,592, 164,838)	198,492 (77,069, 375,464)	175,660 (82,387, 292,889)	0.005 HIE vs. MIE, 0.005 MIE vs. RE, 0.477 HIE vs. RE	40.0 (20.0, 140.0)	20.0 (20.0, 40.0)	40.0 (20.0, 40.0)	0.000 HIE vs. MIE, 0.028 MIE vs. RE, 0.038 HIE vs. RE	100.2 (70.3, 207.1)	185.0 (94.8, 439.3)	217.8 (101.5, 328.3)	0.010 HIE vs. MIE, 0.004 MIE vs. RE, 0.715 HIE vs. RE
Cortisol (nmol/L)	480 (0, 4,888)	6,129 (2,061, 20,954)	4,095 (987, 23,898)	0.000 HIE vs. MIE, 0.003 MIE vs. RE, 0.879 HIE vs. RE	60.0 (40.0, 280.0)	60.0 (40.0, 60.0)	60.0 (40.0, 100.0)	0.088 HIE vs. MIE, 0.346 MIE vs. RE, 0.085 HIE vs. RE	7.8 (0.0, 58.7)	61.8 (31.1, 83.3)	46.0 (23.6, 152.0)	0.000 HIE vs. MIE, 0.001 MIE vs. RE, 0.976 HIE vs. RE
Growth hormone (μg/L)	299 (90, 571)	428 (186, 963)	425 (176, 712)	0.030 HIE vs. MIE, 0.086 MIE vs. RE, 0.516 HIE vs. RE	60.0 (40.0, 80.0)	50.0 (40.0, 220.0)	60.0 (40.0, 220.0)	0.670 HIE vs. MIE, 0.864 MIE vs. RE, 0.682 HIE vs. RE	681 (123, 1494)	1,196 (203, 9100)	972 (274, 4550)	0.024 HIE vs. MIE, 0.112 MIE vs. RE, 0.349 HIE vs. RE
Heart rate (bpm)	2,291 (1,943, 2, 736)	2,684 (2,031, 3,054)	2,302 (1,808, 3,233)	0.107 HIE vs. MIE, 0.720 MIE vs. RE, 0.489 HIE vs. RE	35.0 (33.0, 37.0)	34.0 (33.0, 36.0)	36.0 (27.0, 37.0)	0.503 HIE vs. MIE, 0.572 MIE vs. RE, 0.626 HIE vs. RE	90.3 (67.7, 114.0)	105.1 (91.6, 123.0)	107.5 (85.7, 127.1)	0.007 HIE vs. MIE, 0.015 MIE vs. RE, 0.72 HIE vs. RE
Lactate (mmol/L)	84.4 (45.9, 116.0)	433.2 (294.4, 559.7)	349.9 (225.4, 525.9)	0.000 HIE vs. MIE, 0.000 MIE vs. RE, 0.382 HIE vs. RE	30.0 (20.0, 40.0)	40.0 (20.0, 40.0)	40.0 (40.0, 40.0)	0.478 HIE vs. MIE, 0.047 MIE vs. RE, 0.220 HIE vs. RE	152.4 (97.9, 266.3)	687.0 (473.7, 1007.5)	668.6 (411.8, 960.2)	0.000 HIE vs. MIE, 0.000 MIE vs. RE, 0.626 HIE vs. RE
Ketones (mmol/L)	43.5 (19.6, 69.3)	31.7 (17.8, 74.25)	21.7 (8.7, 53.1)	0.715 HIE vs. MIE, 0.015 MIE vs. RE, 0.318 HIE vs. RE	260.0 (180.0, 280.0)	230.0 (160.0, 280.0)	250.0 (180.0, 280.0)	0.508 HIE vs. MIE, 0.996 MIE vs. RE, 0.642 HIE vs. RE	232.1 (145.5, 380.0)	187.5 (100.0, 260.0)	145.5 (87.5, 250.0)	0.773 HIE vs. MIE, 0.072 MIE vs. RE, 0.321 HIE vs. RE
Insulin (mU/L)	19.6 (0.0, 212.9)	0.00 (0.0, 117.4)	28.9 (0.0, 287.8)	0.435 HIE vs. MIE, 0.759 MIE vs. RE, 0.322 HIE vs. RE	260.0 (40.0, 280.0)	280.0 (160.0, 280.0)	190.0 (40.0, 280.0)	0.357 HIE vs. MIE, 0.207 MIE vs. RE, 0.173 HIE vs. RE	8.7 (0.0, 37.7)	0.0 (0.0, 40.8)	12.7 (0.0, 57.8)	0.637 HIE vs. MIE, 0.759 MIE vs. RE, 0.058 HIE vs. RE

Incremental AUC. Data are median (IQR) unless otherwise indicated. *x refers to relevant parameter units.

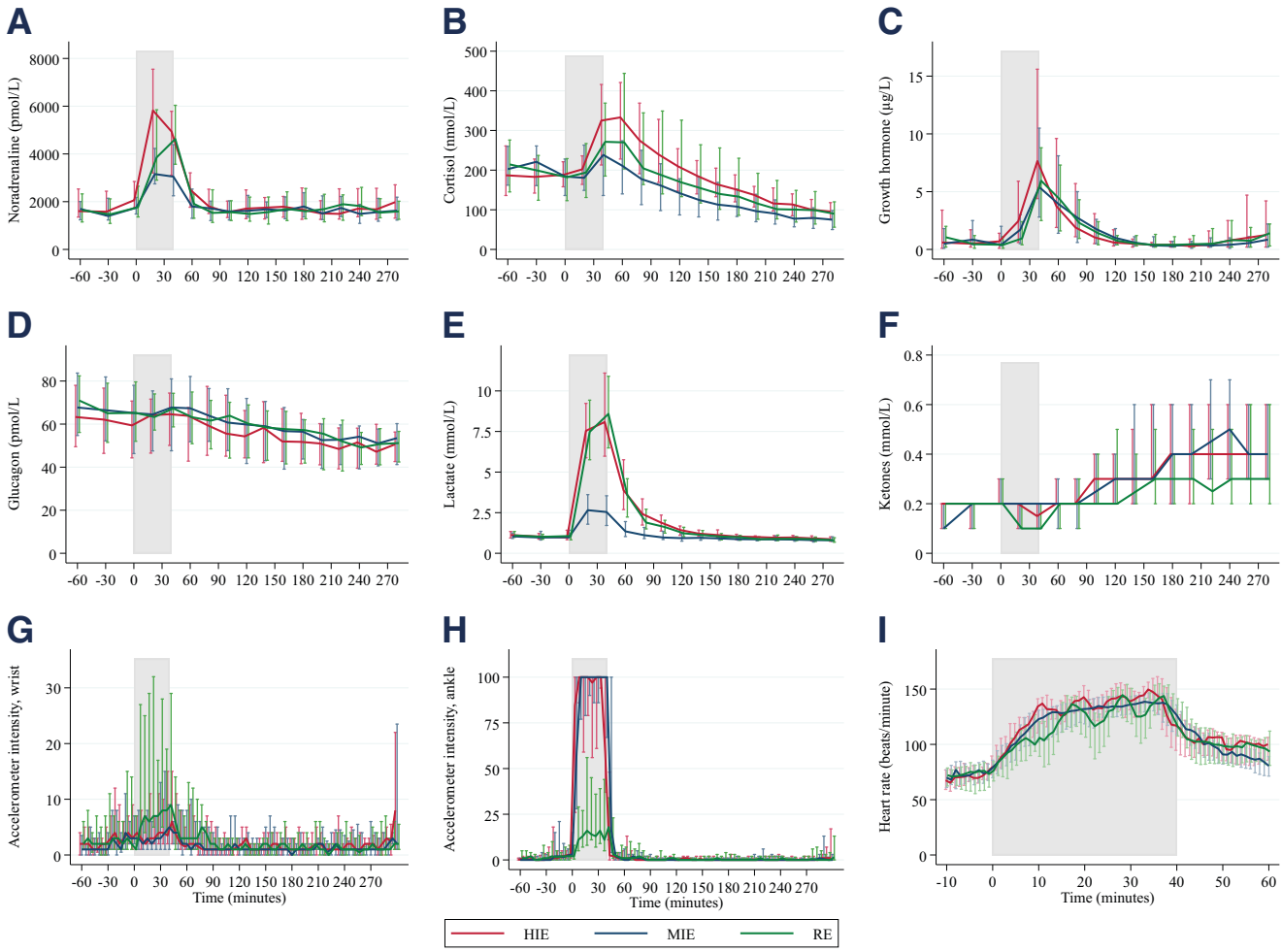

Figure 1—Changes in noradrenaline (*A*), cortisol (*B*), growth hormone (*C*), glucagon (*D*), lactate (*E*), ketones (*F*), accelerometer intensity (wrist) (*G*), accelerometer intensity (ankle) (*H*), and heart rate (*I*) −60 min to 280 min post–exercise commencement. Results shown are median and IQR.

immediately following, exercise commencement would likely have a limited impact on glucose levels in the immediate term. Proactive strategies aimed at reducing the likelihood of hypoglycemia during exercise would remain paramount (29,30). We acknowledge that additional inputs could be used to trigger exogenous glucagon delivery, which is known to help limit the drop in glycemia during MIE (31–33).

The strengths of this study include the randomized crossover design, which included three discrete exercise categories with differing metabolic responses; the use of VO_2peak and max power assessments for standardized exercise prescription; a protocol ensuring a consistent set of rules determining carbohydrate supplementation; insulin delivery with a commercially available closed-loop system; and comprehensive biochemical and kinetic data assessments.

This study also has limitations. The exercise protocols were ∼40 min in duration with forward planning, and thus, our findings have limited applicability to unplanned exercise bouts or those of longer duration. Also, exercise was undertaken in the late afternoon, and we recognize that the diurnal counterregulatory hormone variation and duration of fasting may impact glycemia during exercise (34). While the exercise interventions fell into three discrete categories to aid interpretation of these data, physical activity undertaken as part of everyday living may contain a mixture of each category. In order to limit the impact of meals and bolus insulin upon study observations, participants did not eat for 4 h prior to the exercise and 4 h post-exercise, and thus, the protocol was not reflective of free-living conditions. The system used was a first-generation system, and newer HCL systems may lead to different outcomes. Finally, participant selection recruited a cohort with good glycemic control, which may not be representative of the greater population with type 1 diabetes. However, given that ∼50% of insulin delivered by HCL is user initiated, this ensured that any differences observed in the metabolic responses to the exercise interventions were not confounded by inconsistencies in insulin dosing.

In conclusion, there were no clinically significant differences in glycemic control among the three exercise types, and consensus targets were met with insulin dosing using a first-generation HCL system in individuals with type 1 diabetes and good glycemic control at baseline. Counterregulatory hormone responses to exercise and proactive strategies aimed at reducing the glycemic impact of insulin delivered prior to exercise appear to have the greatest influence on glucose levels during and

immediately following exercise. A strategy incorporating additional signals to negate the need for preset temporary targets or supplemental carbohydrate during and immediately following exercise may not be achievable with current insulin formulations and in the absence of glucagon delivery. Further research is needed to determine if these additional signals may have a beneficial impact in longer duration exercise and in the post-exercise period, particularly postprandially, given the apparent differences in insulin sensitivity related to exercise intensity. We suggest that insulin formulations with onset and offset of action closer to that observed with normal physiology would be a more productive and cost-effective step in the journey toward fully automated closed-loop functionality during exercise.

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