



# Glucose and Counterregulatory Responses to Exercise in Adults With Type 1 Diabetes and Impaired Awareness of Hypoglycemia Using Closed-Loop Insulin Delivery: A Randomized Crossover Study

*Diabetes Care* 2020;43:480–483 | <https://doi.org/10.2337/dc19-1433>

Melissa H. Lee,<sup>1,2</sup> Sara Vogrin,<sup>1</sup>  
Barbora Paldus,<sup>1</sup> Dilshani Jayawardene,<sup>1</sup>  
Hannah M. Jones,<sup>1,2</sup> Sybil A. McAuley,<sup>1,2</sup>  
Varuni Obeyesekere,<sup>2</sup> Judith Gooley,<sup>1</sup>  
André La Gerche,<sup>3,4</sup> Richard J. Maclsaac,<sup>1,2</sup>  
Vijaya Sundararajan,<sup>1,5</sup> Alicia J. Jenkins,<sup>1,2,6</sup>  
Glenn M. Ward,<sup>2,7</sup> and David N. O'Neal<sup>1,2</sup>

## OBJECTIVE

To evaluate exercise-related glucose and counterregulatory responses (CRR) in adults with type 1 diabetes with impaired awareness of hypoglycemia (IAH) using hybrid closed-loop (HCL) insulin delivery to maintain glucose homeostasis.

## RESEARCH DESIGN AND METHODS

Twelve participants undertook 45-min high-intensity intermittent exercise (HIIE) and moderate-intensity exercise (MIE) in random order. The primary outcome was continuous glucose monitoring (CGM) time in range (70–180 mg/dL) for 24-h post-exercise commencement.

## RESULTS

CGM time in range was similar for HIIE and MIE (median 79.5% [interquartile range 73.2, 87.6] vs. 76.1% [70.3, 83.9],  $P = 0.37$ ), and time with levels <54mg/dL post-exercise commencement was 0%. HIIE induced greater increases in cortisol ( $P = 0.002$ ), noradrenaline ( $P = 0.005$ ), and lactate ( $P = 0.002$ ), with no differences in adrenaline, dopamine, growth hormone, or glucagon responses.

## CONCLUSIONS

IAH adults using HCL undertaking HIIE and MIE exhibit heterogeneity in CRR. Novel findings were a preserved cortisol response and variable catecholamine responses to HIIE.

Impaired awareness of hypoglycemia (IAH) affects 20% of adults with type 1 diabetes, with a sixfold increase in severe hypoglycemia (1). IAH-related defects in counterregulatory responses (CRR) have not been fully elucidated. Exercise, like hypoglycemia, elicits complex adaptive CRR to maintain glucose homeostasis (2), differing by exercise type and duration (3). Adults with type 1 diabetes with hypoglycemia awareness (HA) mount a robust CRR in response to exercise, greater for high-intensity intermittent exercise (HIIE) than moderate-intensity exercise (MIE) (4). Exercise-related CRR are not well defined with IAH.

<sup>1</sup>University of Melbourne, Department of Medicine, Melbourne, Australia

<sup>2</sup>Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Melbourne, Australia

<sup>3</sup>Department of Cardiology, St Vincent's Hospital Melbourne, Melbourne, Australia

<sup>4</sup>Clinical Research Domain, Baker Heart and Diabetes Institute, Melbourne, Australia

<sup>5</sup>Department of Public Health, La Trobe University, Melbourne, Australia

<sup>6</sup>NHMRC Clinical Trials Centre at the University of Sydney, Sydney, Australia

<sup>7</sup>Department of Pathology, University of Melbourne, Melbourne, Australia

Corresponding author: David N. O'Neal, [dno@unimelb.edu.au](mailto:dno@unimelb.edu.au)

Received 21 July 2019 and accepted 3 November 2019

Clinical trial reg. no. ACTRN12618000070235, [www.anzctr.org.au](http://www.anzctr.org.au)

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1433/-/DC1>.

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

This study evaluated exercise-related glucose control and CRR in adults with IAH employing hybrid closed-loop (HCL) insulin delivery to mitigate confounding hypoglycemia.

## RESEARCH DESIGN AND METHODS

HCL-naive adults with type 1 diabetes (>18 years) with IAH (Gold score  $\geq 4$ ) (5) were recruited. IAH severity was assessed with Gold and Clarke questionnaires (5,6).

An ethics-approved randomized HIIE versus MIE crossover study using HCL (MiniMed 670G insulin pump and Guardian 3 glucose sensor [Medtronic, Northridge, CA]) was conducted at St Vincent's Hospital Melbourne.

Participants were educated and provided study devices. There was  $\geq 1$ -week run-in with HCL activated pre-HIIE and -MIE, conducted in random order. A minimum 1-week washout period separated exercise bouts.

Exercise parameters were individualized using cardiopulmonary fitness measurements (7). Participants undertook two 45-min exercise bouts (equal energy expenditure) on an upright cycle ergometer: 1) HIIE: six 4-min bouts of near-maximal exercise (intensity halfway between anaerobic threshold [AT] and maximal exercise capacity) with 2-min rest after each interval and an additional 4-min rest between third and fourth intervals, and 2) MIE: 40 min at 70% anaerobic threshold.

Participants inserted a new glucose sensor and insulin line 24 h pre-exercise and abstained from vigorous exercise for 48 h pre-study. On the exercise day (Supplementary Fig. 1), participants consumed breakfast ( $\sim 40$  g carbohydrate at 0700 h) with their usual insulin dose bolused. On arrival at the hospital (2 h pre-exercise at 0900 h), the HCL target was increased from 120 to 150 mg/dL until 15 min post-exercise completion. Supplemental carbohydrate, without an insulin bolus, was administered 15 min pre-exercise if the glucose level was  $\leq 126$  mg/dL (8). Exercise commenced if the glucose level was  $>90$  mg/dL. Venous sampling commenced every 15 min from 60 min pre-exercise until 120 min post-exercise completion for glucose, lactate, ketones, adrenaline, noradrenaline, dopamine, cortisol, growth hormone (GH), and glucagon as measured previously (4).

Poststudy, participants were provided lunch and then returned home.

The primary outcome was continuous glucose monitoring (CGM) time in range (70–180 mg/dL) for 24 h post-exercise commencement. Secondary outcomes included biochemical and CGM changes (9).

Results are median (interquartile range [IQR]) or frequency (percentage) unless otherwise specified with significance at  $P < 0.05$ . CGM and incremental area under the curve (AUC) from exercise commencement to 120 min post-exercise completion (0–165 min) were compared between HIIE and MIE using Wilcoxon signed rank test. A post hoc exploratory analysis compared CRR data from this study with published data from an HA group undertaking identical exercise protocols with HCL insulin delivery (4). Increments from baseline to peak value comparisons between IAH and HA group used rank sum tests separately for each exercise type. All analyses were performed using Stata 15.1.

## RESULTS

Twelve adults completed the study: six men and six women, age 53 years (42, 57),  $HbA_{1c}$  7.2% (6.5, 7.4) (55 mmol/mol [48, 57]), diabetes duration 28 years (18, 38), Gold score 6 (5, 7), and Clarke score 6 (6, 7) (Supplementary Table 1). Supplemental carbohydrate was required by six and four participants pre-HIIE and pre-MIE, respectively. One participant experienced asymptomatic hypoglycemia (nadir 57 mg/dL) during MIE.

Over the 24-h post-exercise commencement (Supplementary Table 2 and Supplementary Fig. 2), CGM time in range was 79.5% (73.2, 87.6) vs. 76.1% (70.3, 83.9) ( $P = 0.37$ ), with minimal hypoglycemia (time spent with levels  $<70$  mg/dL, HIIE 0.0% [0.0, 0.0], MIE 0.4% [0.0, 3.4],  $P = 0.045$ ; time  $<54$  mg/dL, for both groups 0.0% [0.0, 0.0]). During exercise (0–45 min), time in range for HIIE and MIE was 100% (90, 100) vs. 100% (75, 100), respectively ( $P = 0.54$ ). There was a trend toward a greater plasma glucose increment (Fig. 1A) with HIIE versus MIE (AUC 29.16 mg/dL \* min [0.00, 67.14] vs.  $-19.80$  mg/dL \* min [ $-27.54$ , 52.56],  $P = 0.07$ ). Twenty-four hours pre-exercise, time  $<54$  mg/dL was 0%, with no severe hypoglycemia (Supplementary Table 2).

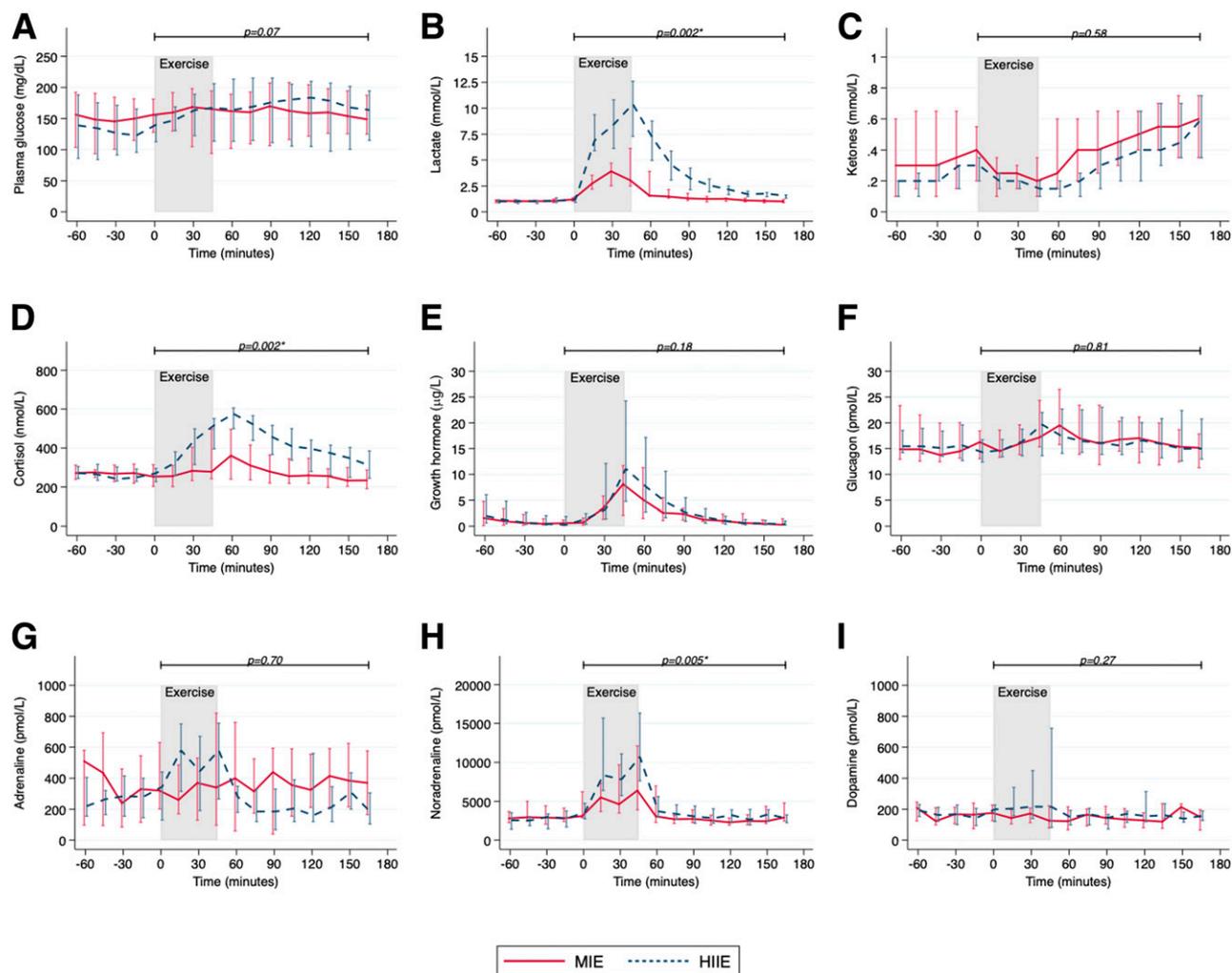
Lactate increment (Fig. 1B) was greater with HIIE versus MIE (AUC 3.56 mmol/L \* min [2.37, 4.36] vs. 0.78 mmol/L \* min [0.29, 1.44], respectively;  $P = 0.002$ ), peaking at exercise completion. Ketones (Fig. 1C) changed similarly over time, decreasing during exercise and then peaking 120 min postcompletion.

Cortisol increment (Fig. 1D) was greater with HIIE versus MIE (AUC nmol/L \* min 166.8 [111.5, 195.7] vs. 26.0 nmol/L \* min [ $-48.2$ , 93.9], respectively;  $P = 0.002$ ), peaking 15 min postcompletion. No differences in increments of GH (Fig. 1E) (AUC 0.80  $\mu$ g/L \* min [ $-0.07$ , 7.34] vs. 1.15  $\mu$ g/L \* min [ $-0.06$ , 3.42], respectively;  $P = 0.18$ ) or glucagon (Fig. 1F) (AUC 0.80 pmol/L \* min [0.05, 1.93] vs. 1.24 pmol/L \* min [0.52, 1.63], respectively;  $P = 0.81$ ) were observed for HIIE vs. MIE. Adrenaline increment was similar for HIIE versus MIE (Fig. 1G) (AUC 63.1 pmol/L \* min [ $-78.3$ , 145.8] vs. 43.7 pmol/L \* min [ $-73.6$ , 151.0], respectively;  $P = 0.70$ ). Noradrenaline increment (Fig. 1H) was greater with HIIE versus MIE (AUC 2,281.4 pmol/L \* min [1,334.5, 2,466.7] vs. 657.0 pmol/L \* min [ $-807.4$ , 902.4], respectively;  $P = 0.005$ ), peaking at exercise completion. Dopamine increment (Fig. 1I) was similar for HIIE versus MIE (AUC 32.1 pmol/L \* min [ $-47.3$ , 140.8] vs.  $-8.4$  pmol/L \* min [ $-46.8$ , 34.9], respectively;  $P = 0.27$ ), peaking 30 min post-exercise commencement.

Post hoc comparisons of exercise-related CRR between HA (4) and IAH groups (Supplementary Fig. 3) revealed reductions in peak adrenaline responses with HIIE ( $P < 0.001$ ) and dopamine responses with MIE ( $P = 0.009$ ) in IAH. Other catecholamine and GH responses were blunted in IAH but did not reach significance. In contrast, the cortisol response was preserved in IAH compared with HA in response to HIIE ( $P = 0.36$ ) and MIA ( $P = 0.45$ ).

## CONCLUSIONS

This study is the first to comprehensively compare CRR during HIIE and MIE (confirmed by lactate differences) in adults with severe IAH using HCL insulin delivery to minimize hypoglycemia. While previous studies demonstrate blunting of metabolic responses to MIE following antecedent hypoglycemia (2,10), IAH studies comparing responses to HIIE and



**Figure 1**—Profiles of plasma glucose (A), lactate (B), ketones (C), cortisol (D), GH (E), glucagon (F), adrenaline (G), noradrenaline (H), and dopamine (I) from 60 min prior to exercise commencement to 120 min following exercise completion, comparing HIIE and MIE exercise stages. Exercise period represented by shaded box. Values are median and IQR. \*Statistically significant results.

MIE, while controlling for hypoglycemia, are lacking. Our study had minimal antecedent and exercise-associated hypoglycemia; therefore, any differences in CRR observed with HIIE versus MIE were likely attributable to exercise itself.

Although it was not powered, we performed a post hoc comparison between this IAH cohort and our prior work in a HA group (4). Both included 12 pump-experienced adults using identical HCL systems and exercise interventions. Subjects with IAH were older (53 vs. 36 years), had higher Gold scores (6 vs. 2), lower HbA<sub>1c</sub> levels (7.2% [55 mmol/mol] vs. 7.6% [60 mmol/mol]), longer duration of diabetes (27.5 vs. 23.5 years), and lower fitness levels (VO<sub>2max</sub> 25.6 vs. 32.4 mL/kg/min).

Generally, differences in catecholamine responses to exercise were blunted in IAH, with an adrenaline increment of ~150%

with HIIE in IAH versus ~350% increment in HA (4). Interestingly, Hwang et al. (11) compared hypoglycemia-induced adrenaline responses with and without IAH, demonstrating a 60–70% increment with IAH and 300% increment with HA. In contrast to adrenaline, we found noradrenaline responses to HIIE were relatively preserved in IAH, similar to findings by Hwang et al. (11) with hypoglycemia. We acknowledge that Gold and Clarke scores are subjective and may have contributed to the heterogeneity in catecholamine responses. Fitter individuals can also mount higher catecholamine responses at maximal intensity (12), which may partly explain the more robust responses with HA.

The preserved cortisol response with IAH, suggesting an intact exercise-induced hypothalamic-pituitary-adrenal axis activation, is novel. It is hypothesized that IAH is

a consequence of alterations in central glucose-sensing neurons modulating CRR coordination and hypoglycemia responses (13). Our findings suggest heterogeneity according to the counterregulatory hormone in question, implying only partial commonality in the central pathways compromising CRR to both exercise and hypoglycemia with IAH. It is of interest that early IAH studies showed partial restoration of defective CRR to hypoglycemia following a single HIIE bout (14,15). Exploration of recurrent HIIE bouts as a dishabituating stimulus to restore HA is warranted.

In conclusion, in IAH, partial preservation with heterogeneity of CRR to exercise was observed, with novel findings of a preserved cortisol response and variable catecholamine responses to HIIE. The underlying physiology and

mechanisms of the metabolic and hormonal changes during exercise require further elucidation.

**Acknowledgments.** The authors thank the participants who contributed time to this study. The authors acknowledge Dr. Rinky Giri (Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Melbourne, Australia) for her time in assisting with study visits; Dr. Robert Vigersky, Dr. Natalie Kurtz, Dr. Benjamin Grosman, and Dr. Anirban Roy (Medtronic, Northridge, California) for providing technical support; and Ca-triona Sims (University of Melbourne Department of Medicine, Melbourne, Australia) and Marion Jamieson (Medtronic, Melbourne, Australia) for providing logistical support.

**Funding.** This investigator-initiated study was funded by a Diabetes Australia Research Program grant (Diabetes Australia Research Trust) and a St Vincent's Hospital Melbourne Research Endowment Fund grant. Material support was provided from Medtronic. M.H.L. is supported by a National Health and Medical Research Council (NHMRC) postgraduate scholarship, cofunded by Diabetes Australia. B.P. is supported by a University of Melbourne scholarship and research support from JDRF. S.A.M. is supported by a JDRF Early-Career Diabetes Research Award. A.J.J. is supported by a NHMRC Practitioner Grant and is a Sydney Medical School Foundation Fellow.

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

**Duality of Interest.** M.H.L. and B.P. have received speaker honoraria from Medtronic. S.A.M. has received support for research from Medtronic. R.J.M. has received support for research and honoraria from Medtronic, Novo Nordisk, Eli Lilly, and Sanofi. A.J.J. has been on advisory boards for Medtronic, Sanofi and Abbott. D.N.O. has been on advisory boards and has received support for research and honoraria from Medtronic, Novo,

Sanofi and Abbott. No other potential conflicts of interest relevant to this article were reported.

**Prior Presentation.** Parts of this study were presented in abstract form at the 12th International Conference on Advanced Technologies & Treatments for Diabetes, Berlin, Germany, 20–23 February 2019.

## References

- Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. *Diabet Med* 2008;25:501–504
- Galassetti P, Tate D, Neill RA, Richardson A, Leu S-Y, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. *Am J Physiol Endocrinol Metab* 2006;290:E1109–E1117
- Bally L, Laimer M, Stettler C. Exercise-associated glucose metabolism in individuals with type 1 diabetes mellitus. *Curr Opin Clin Nutr Metab Care* 2015;18:428–433
- Jayawardene DC, McAuley SA, Horsburgh JC, et al. Closed-loop insulin delivery for adults with type 1 diabetes undertaking high-intensity interval exercise versus moderate-intensity exercise: a randomized, crossover study. *Diabetes Technol Ther* 2017;19:340–348
- Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994;17:697–703
- Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–522
- Balady GJ, Arena R, Sietsema K, et al.; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225
- Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017;5:377–390
- Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. *Diabetes Care* 2016;39:1175–1179
- Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in type 1 diabetes. *Diabetes* 2003;52:1761–1769
- Hwang JJ, Parikh L, Lacadie C, et al. Hypoglycemia unawareness in type 1 diabetes suppresses brain responses to hypoglycemia. *J Clin Invest* 2018;128:1485–1495
- Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. *Sports Med* 2008;38:401–423
- Tesfaye N, Seaquist ER. Neuroendocrine responses to hypoglycemia. *Ann N Y Acad Sci* 2010;1212:12–28
- McNeilly AD, Gallagher JR, Huang JT, Ashford MLJ, McCrimmon RJ. High-intensity exercise as a dishabituating stimulus restores counterregulatory responses in recurrently hypoglycemic rodents. *Diabetes* 2017;66:1696–1702
- Farrell CM, West DJ, Hapca SM, Jones T, McNeilly AD, McCrimmon RJ. ADA presidents' select abstract: dishabituating with high intensity exercise improves epinephrine response and symptomatic awareness to hypoglycemia in people with type 1 diabetes and impaired awareness of hypoglycemia (Abstract). *Diabetes* 2019;68(Suppl. 1):113-OR