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First Randomized Controlled Trial of Hybrid Closed Loop Versus Multiple Daily Injections or Insulin Pump Using Self-Monitoring of Blood Glucose in Free-Living Adults with Type 1 Diabetes Undertaking Exercise

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The JDRF Australia Adult Hybrid Closed Loop (HCL) Study Group recently published results of the first randomized trial (ACTRN12617000520336, HREC-D088/16) of the commercially available HCL MiniMed™ 670G system (Medtronic, Northridge, CA).[1,2] The trial compared six-months HCL vs. standard therapy [self-monitoring of blood glucose (SMBG) with multiple-daily-injections or continuous subcutaneous insulin infusion (CSII) without continuous glucose monitoring (CGM)] in adults with type 1 diabetes. It demonstrated that HCL improves glucose management, including time-in-range (70-180 mg/dl), all other CGM metrics, HbA1c and 1,5 anhydroglucitol.[1] As there is limited evidence regarding HCL use with exercise[3] we conducted a sub-study comparing glucose management in 10 adults with type 1 diabetes undertaking 45 min of moderate-intensity exercise (MIE) and high-intensity interval exercise (HIIE) in random order separated by 7-days, with 6 subjects (computer) randomized to HCL and 4 to standard therapy. After 5 min warm-up (25% VO2max) MIE comprised 40 min of continuous exercise at 70% of their anerobic threshold. HIIE comprised 6 repetitions of 4 min at intensity half-way between anerobic threshold and maximal capacity, separated by 2 to 4 min rest. HCL participants implemented an increased glucose target of 150 mg/dL (from 120 mg/dL) 1 h pre-exercise until 15 min post-exercise.

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Table 1. Glucose metrics 0 to 24 h and 0 to 2 h post-exercise commencement with standard therapy versus HCL for both exercise types combined and for moderate intensity exercise (MIE) and high intensity exercise (HIIE).

	Combined analysis (MIE and HIIE)			MIE			HIIE		
Glucose metrics	Standard therapy ($n=4$)	Hybrid closed-loop ($n=6$)	*P* value	Standard therapy ($n=4$)	Hybrid closed-loop ($n=5^{\dagger}$)	*P* value	Standard therapy ($n=4$)	Hybrid closed-loop ($n=6$)	*P* value
0-24 h post-exercise									
% time 70-180 mg/dL (3.9-10 mmol/L)	46.5 (33.9, 57.7)	69.7 (62.3, 82.3)	.033*	45.5 (32.0, 52.6)	66.7 (63.5, 70.8)	.027*	60.4 (34.4, 64.1)	75.0 (72.5, 90.6)	.055
% time 70-140 mg/dL (3.9-7.8 mmol/L)	25.5 (14.7, 40.2)	50.9 (41.2, 55.2)	.033*	33.3 (18.9, 36.1)	43.8 (38.5, 60.4)	.086	27.1 (9.4, 45.3)	57.6 (41.1, 66.7)	.042*
% time <70 mg/dL (<3.9 mmol/L)	5.5 (4.2, 12.6)	3.5 (1.6, 5.7)	.24	10.9 (6.9, 21.5)	0.0 (0.0, 3.7)	.046*	1.6 (0.0, 5.2)	5.0 (0.0, 10.0)	.38
% time <54 mg/dL (<3.0 mmol/L)	1.6 (0.8, 6.1)	0.6 (0.0, 1.6)	.28	3.1 (1.6, 12.1)	0.0 (0.0, 0.0)	.041*	0.0 (0.0, 0.0)	0.0 (0.0, 3.1)	.22
% time >180 mg/dL (>10 mmol/L)	46.1 (30.0, 61.7)	25.0 (15.6, 31.7)	.055	36.5 (27.7, 59.3)	33.3 (25.0, 36.5)	.62	38.0 (32.3, 64.1)	15.0 (9.4, 17.7)	.055
Mean glucose (mg/dL)	173.0 (151.7, 197.5)	144.7 (142.4, 146.9)	.033*	161.3 (147.2, 196.0)	161.6 (146.7, 164.7)	.46	170.5 (156.2, 198.9)	126.4 (120.4, 147.1)	.033*
Coefficient of variation (%)	32.8 (30.1, 50.5)	33.7 (32.1, 41.5)	.83	43.3 (34.1, 66.3)	40.2 (31.6, 41.3)	.33	29.4 (16.9, 44.0)	35.9 (25.9, 42.9)	.83
0-2 h post-exercise									
% time 70-180 mg/dL (3.9-10 mmol/L)	29.6 (25.0, 52.3)	100.0 (86.4, 100.0)	.13	31.8 (9.1, 54.6)	100.0 (100.0, 100.0)	.007*	40.9 (18.2, 72.7)	100.0 (72.7, 100.0)	.25
% time 70-140 mg/dL (3.9-7.8 mmol/L)	15.9 (0.0, 43.2)	50.0 (36.4, 63.6)	.21	22.7 (0.0, 54.6)	63.6 (63.6, 81.8)	.080	0.0 (0.0, 31.8)	9.1 (9.1, 45.5)	.25
% time <70 mg/dL (<3.9 mmol/L)	9.1 (0.0, 22.7)	0.0 (0.0, 0.0)	.24	18.2 (0.0, 45.5)	0.0 (0.0, 0.0)	.094	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	.37
% time <54 mg/dL (<3.0 mmol/L)	4.6 (0.0, 9.1)	0.0 (0.0, 0.0)	.091	9.1 (0.0, 18.2)	0.0 (0.0, 0.0)	.091	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	N/A
% time >180 mg/dL (>10 mmol/L)	61.4 (25.0, 75.0)	0.0 (0.0, 4.6)	.37	40.9 (0.0, 90.9)	0.0 (0.0, 0.0)	.094	59.1 (27.3, 81.8)	0.0 (0.0, 9.1)	.25
Mean glucose (mg/dL)	173.0 (117.9, 232.0)	136.4 (129.2, 148.3)	.46	157.9 (72.2, 275.8)	137.7 (121.5, 141.5)	1.00	187.9 (149.2, 202.7)	151.4 (124.2, 155.0)	.14
Coefficient of variation (%)	20.1 (11.7, 23.4)	8.7 (7.7, 9.4)	.62	24.5 (9.1, 33.0)	8.2 (7.6, 12.9)	.33	13.6 (5.9, 22.2)	7.2 (6.6, 11.1)	.81

*Statistically significant results.
†Masked CGM data missing due to sensor failure.

Participants in the standard therapy group, reduced morning basal insulin injections by 30% and CSII basal rates by 70% from 1 h pre-exercise to 15 min post-exercise. If pre-exercise SMBG was <90 mg/dL or <126 mg/dL, 10 g and 20 g carbohydrate was consumed, respectively.[4] This was required by one standard group subject before both MIE and HIIE. Venous glucose, ketones, lactate and counter-regulatory hormones were assessed in samples collected at 15 min intervals from 60 min pre- to 210 min post-exercise.[5] The primary outcome was masked CGM time-in-range 70 to 180 mg/dL for 24 h post-exercise commencement. Secondary outcomes were CGM metrics for 24 h and 2 h post-exercise, ketones, lactate, and counter-regulatory hormones.[6] All 10 participants (seven women, aged 46 years [37, 53], 32 years [26, 40] of diabetes, HbA1c: 7.9% [7.4, 8.6] / 63mmol/mol [57, 70] and VO2max: 22.7 mL/kg/min [19.4, 28.2]), completed the study.

In an analysis combining MIE and HIIE, HCL improved time-in-range 0 to 24 h post-exercise commencement (69.7% [62.3, 82.3] vs. 46.5% [33.9, 57.7]; $P=.033$). For MIE (0-24 h) time-in-range was greater, and time-below-range was lower for HCL (Table 1).

From 0 min to 2 h post-exercise (0-2 h), time-in-range and time below range for HCL vs. standard therapy for the combined exercise groups and for HIIE did not differ significantly. For MIE (0-2 h), time-in-range was greater for HCL vs. standard therapy (100% [100, 100] vs. 31.8% [9.1, 54.6]; $P=0.007$), while time-below range did not differ significantly. (Table 1) There were no differences between HCL and standard therapy in ketones, lactate, cortisol, adrenaline, noradrenaline, and dopamine with MIE or HIIE (data not shown).

One HCL participant experienced hypoglycemia (SMBG 54 mg/dL) during MIE and one HCL participant within 120 min post-MIE (SMBG 67 mg/dL). There were no episodes of severe hypoglycaemia or other serious adverse events.

In conclusion, relative to standard therapy during MIE and HIIE and up to 24 h post exercise, HCL use significantly improves time-in-range by 23% with no increase in hypoglycemia. Larger home-based studies are warranted.

Abbreviations

CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; HCL: hybrid closed loop; HIIE: high-intensity interval exercise; MIE: moderate-intensity exercise; SMBG: self-monitoring of blood glucose.

Declaration of Conflicting Interests

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References

1. McAuley SA, Lee MH, Paldus B, et al. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: a randomized, controlled trial. *Diabetes Care*. 2020;43(12):3024-3033.
2. McAuley SA, de Bock MI, Sundararajan V, et al. Effect of 6 months of hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol. *BMJ Open*. 2018;8(6):e020274.
3. Zaharieva DP, Messer LH, Paldus B, O'Neal DN, Maahs DM, Riddell MC. Glucose control during physical activity and exercise using closed loop technology in type 1 diabetes. *Can J Diabetes* 2020;44(8):740-749.
4. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017;5(5):377-390.
5. Lee MH, Vogrin S, Paldus B, et al. Glucose and counterregulatory responses to exercise in adults with type 1 diabetes and impaired awareness of hypoglycaemia using closed-loop insulin delivery: a randomized crossover study. *Diabetes Care*. 2020;43(2):480-483.
6. Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. *Diabetes Care*. 2016;39(7):1175-1179.