Mini-Dose Glucagon as a Novel Approach to Prevent Exercise-Induced Hypoglycemia in Type 1 Diabetes

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OBJECTIVE

Patients with type 1 diabetes who do aerobic exercise often experience a drop in blood glucose concentration that can result in hypoglycemia. Current approaches to prevent exercise-induced hypoglycemia include reduction in insulin dose or ingestion of carbohydrates, but these strategies may still result in hypoglycemia or hyperglycemia. We sought to determine whether mini-dose glucagon (MDG) given subcutaneously before exercise could prevent subsequent glucose lowering and to compare the glycemic response to current approaches for mitigating exercise-associated hypoglycemia.

RESEARCH DESIGN AND METHODS

We conducted a four-session, randomized crossover trial involving 15 adults with type 1 diabetes treated with continuous subcutaneous insulin infusion who exercised fasting in the morning at ∼55% VO_{2max} for 45 min under conditions of no intervention (control), 50% basal insulin reduction, 40-g oral glucose tablets, or 150-μg subcutaneous glucagon (MDG).

RESULTS

During exercise and early recovery from exercise, plasma glucose increased slightly with MDG compared with a decrease with control and insulin reduction and a greater increase with glucose tablets ($P < 0.001$). Insulin levels were not different among sessions, whereas glucagon increased with MDG administration ($P < 0.001$). Hypoglycemia (plasma glucose <70 mg/dL) was experienced by six subjects during control, five subjects during insulin reduction, and none with glucose tablets or MDG; five subjects experienced hyperglycemia (plasma glucose ≥250 mg/dL) with glucose tablets and one with MDG.

CONCLUSIONS

MDG may be more effective than insulin reduction for preventing exercise-induced hypoglycemia and may result in less postintervention hyperglycemia than ingestion of carbohydrate.

Regular physical activity is important for maintaining physical fitness and a healthy body mass while reducing the risk for cardiovascular disease. In patients with type 1 diabetes, regular physical activity and structured exercise is associated with a lower HbA_{1c} level; reduced insulin requirements; a healthy body weight; and reduced prevalence of retinopathy, microalbuminuria, hypertension, and dyslipidemia (1). Unfortunately,

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*A complete list of the T1D Exchange Mini-Dose Glucagon Exercise Study Group can be found in the Supplementary Data online.

See accompanying article, p. 1842.

the majority of patients with type 1 diabetes are sedentary, exercising less than 30 min a day, and most now meet the criteria for being overweight or obese (1). Accordingly, current guidelines recommend that all adults with type 1 diabetes engage in 150 min or more of moderate-to-vigorous intensity physical activity spread out over at least 3 days weekly (2). However, exercise-associated hypoglycemia and the complexity of management aimed at its prevention represent major barriers to the adoption of regular physical activity for many individuals with type 1 diabetes (3–7). Although carbohydrate ingestion can help ameliorate hypoglycemia in patients with type 1 diabetes, patients' carbohydrate requirements can be as high a 1 g/min of exercise (8), which can be counterproductive from a weight management perspective.

Aerobic exercise, in particular, often results in a drop in blood glucose concentration for patients with type 1 diabetes that can result in hypoglycemia. Normally during aerobic exercise endogenous insulin secretion decreases and glucagon secretion increases, which stimulates hepatic glucose production to match the increased rate of glucose disposal in working muscles and to prevent hypoglycemia. In type 1 diabetes, the exogenously delivered insulin typically does not decrease in the circulation during exercise and may in fact increase with accelerated mobilization of insulin from subcutaneous depots, whereas glucagon levels fail to increase (9). The failure of glucagon secretion to increase during exercise is worsened by a recent exposure to hypoglycemia (10). This can create a vicious cycle of repeat hypoglycemic episodes and subsequent counter regulatory failure during both exercise and subsequent hypoglycemia (11). Thus, the prevention of exercise-induced hypoglycemia is also critical for avoiding future episodes of hypoglycemia.

Current approaches to preventing exercise-induced hypoglycemia include reduction in insulin dose and/or the ingestion of carbohydrates, but these strategies may still result in hypoglycemia or hyperglycemia (12–14). Modestly increasing glucagon levels at the start of exercise has not previously been evaluated since current commercially available glucagon preparations are unstable in solution and come as a lyophilized powder that must be reconstituted in diluent immediately prior to injection, and are only indicated at an emergency dose of 1 mg (1,000 μg) for rescue from severe hypoglycemia. A nonaqueous liquid form of glucagon is currently in development with appropriate dose-dependent pharmacokinetic and pharmacodynamics responses when administered subcutaneously at doses of 75, 150, and 300 μg in adults with type 1 diabetes (15). A recent study demonstrated that 150 μg of this mini-dose glucagon (MDG) product was as effective as oral glucose tablets in correcting nonsevere hypoglycemia in adults with type 1 diabetes, enabling the avoidance of unnecessary caloric intake (16). In the current study, we sought to determine whether MDG given subcutaneously before aerobic exercise could prevent subsequent glucose lowering in adults with type 1 diabetes compared with no intervention and further to evaluate the glycemic responses seen with insulin reduction and glucose tablets approaches for mitigating exercise-associated hypoglycemia.

RESEARCH DESIGN AND METHODS

The study was conducted at two academic medical centers within the T1D Exchange Clinic Network (17) under an investigational new drug application from the U.S. Food and Drug Administration. The institutional review board of each center approved the study protocol, and written informed consent was obtained from each participant. Participants included men and women who were 18–64 years of age, had type 1 diabetes of at least 2 years duration, had low C-peptide (random level <0.6 ng/mL) levels, were receiving continuous subcutaneous insulin infusion (continuous subcutaneous insulin infusion or "pump") therapy, were exercising regularly ($\geq$30 min of moderate-to-vigorous aerobic activity at least three times weekly), and were maintaining a BMI of <30 kg/m^2. Exclusion criteria included history of a severe hypoglycemic episode in the 12 months prior to study enrollment, active diabetic retinopathy, peripheral neuropathy with insensate feet, cardiovascular autonomic neuropathy, use of β-blockers or noninsulin antihyperglycemic agents, or currently following a weight-loss diet. Additional protocol details are available at ClinicalTrials.gov (Clinical trial reg. no. NCT02660242).

Prior to participating in the exercise sessions, enrolled subjects underwent assessment of their VO_{2max} during completion of a standardized Bruce protocol. Subjects' insulin pumps and glucometers were downloaded for insulin-dosing review and potential adjustment of basal rates. Each participant completed four exercise sessions, which were scheduled at least 3 days apart and completed within a 12-week period. Subjects were instructed to avoid any vigorous exercise within 24 h before or after participating in each exercise session. The day before each exercise session, subjects inserted a new insulin infusion set into their abdomen or upper buttock as well as placed a new subcutaneous glucose sensor for continuous glucose monitoring (CGM). CGM measures interstitial glucose every 5 min for subsequent download and analysis. Non-CGM users were provided with a blinded Dexcom G4 Platinum CGM to wear during the study. Subjects were in close communication with the study team through the day and night before each exercise session for glycemic management advice, including that for hypoglycemia avoidance.

On the day of the exercise sessions, subjects arrived at the research center by 0900 h after fasting overnight for at least 8 h (see Supplementary Fig. 1 for exercise session flowchart). Conservative administration of glucose tablets was permitted if the blood glucose concentration was <100 mg/dL overnight or in the morning, and a conservative correctional insulin bolus was permitted if the blood glucose concentration was >140 mg/dL first thing in the morning. An intravenous catheter was placed approximately an hour prior to the start of exercise for blood collection. The plasma glucose concentration was required to be 100–140 mg/dL before starting the exercise session, with the last correctional dose of insulin taken at least 3 h earlier, or the session was rescheduled. Exercise consisted of moderate-intensity aerobic activity achieved by brisk walking on a treadmill inclined to maintain the heart rate at 50–55% of maximum as determined by the previous VO_{2max} test. The treadmill speed and slope used during the first exercise session was matched identically during each subsequent exercise session to ensure that subjects completed the same workload during each session.

Subjects completed the four exercise sessions under each of the following four conditions (with the order being randomized): no intervention (control), basal insulin

reduction, administration of oral glucose tablets, or administration of MDG (G-Pen Mini; Xeris Pharmaceuticals, Inc., Austin, TX). All interventions were administered 5 min before the start of exercise. During the control condition, subjects received a sham, single-blind adjustment to their basal rate and a single-blind subcutaneous injection of a saline placebo. During the insulin reduction condition, subjects received a single-blind basal rate reduction to 50%, which returned to the usual rate 45 min after the start of exercise, and a single-blind subcutaneous injection of saline. During the glucose tablets condition, subjects received 20 g of glucose tablets orally and another 20 g at 30 min of exercise (total 40 g). During the MDG condition, subjects

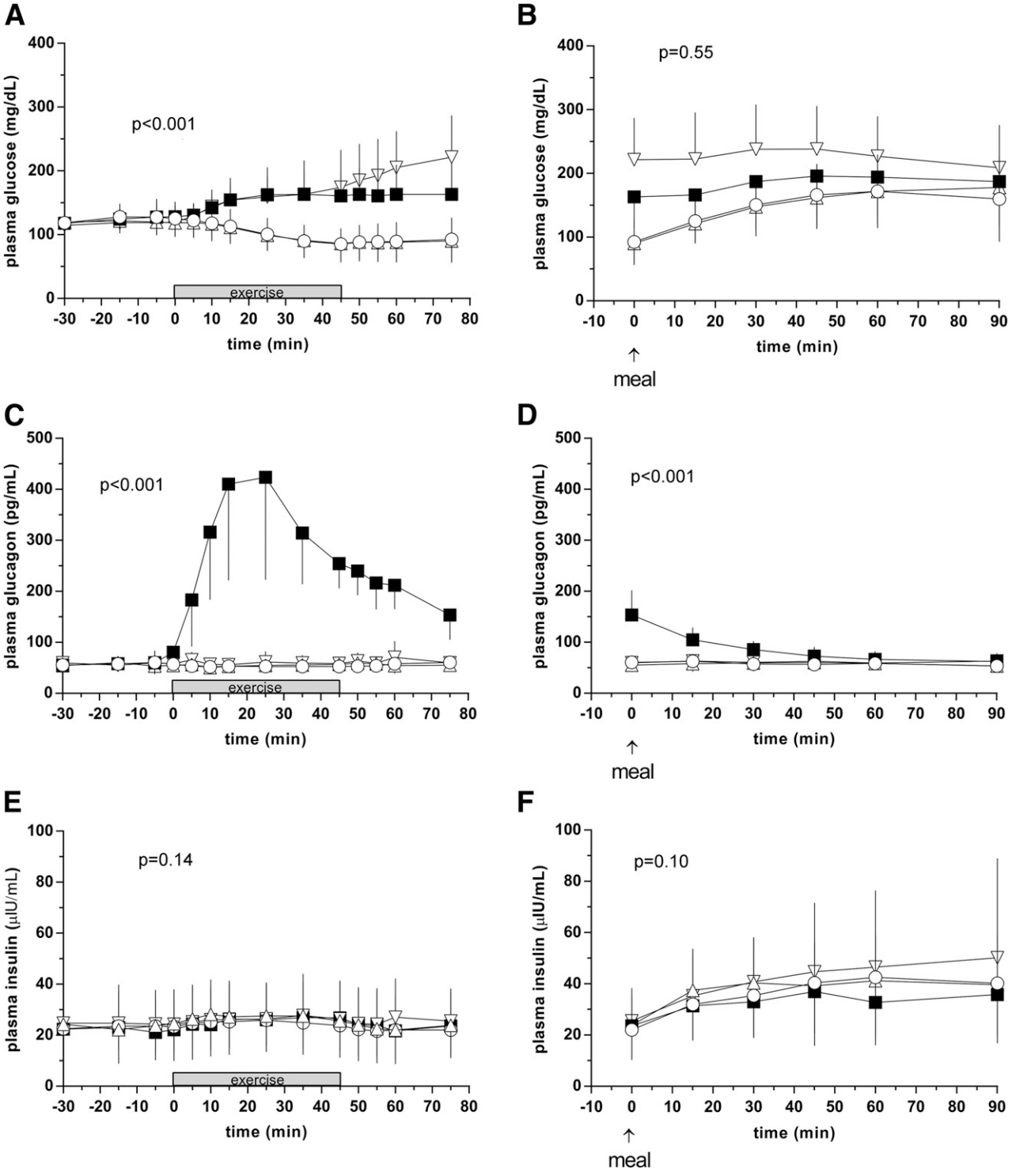

Figure 1—Plasma glucose (*A* and *B*), glucagon (*C* and *D*), and insulin (*E* and *F*) during exercise and early recovery (*A*, *C*, and *E*) and during the subsequent ingestion of a standardized meal (*B*, *D*, and *F*). Treatment with glucose tablets (▽), MDG (-■-), insulin reduction (-○-), or no intervention (control; △) occurred 5 min prior to the start of exercise, and an insulin bolus was administered using each participant's insulin-to-carbohydrate ratio 5 min prior to meal ingestion. Data are the mean ± SD.

received a single-blind sham adjustment to their basal rate and a single-blind subcutaneous injection of 150 μg of glucagon. Thus, the ingestion of glucose tablets was the only condition not single blinded to the participant. The dose of MDG was selected based on a recently published dose-finding study (15) demonstrating effective correction of mild insulin-induced hypoglycemia in patients with type 1 diabetes and was pilot tested in six subjects using the eligibility criteria and exercise intervention of the study protocol (data not shown). The randomization sequence was generated centrally by the coordinating center and revealed to the research center staff using a central study website the morning of the first exercise session.

Blood samples were collected at $t = -30$, -15, -5, and 0 min relative to the start of exercise; at $t = 5$, 10, 15, 25, 35, and 45 min during exercise; and at $t = 50$, 55, 60, and 75 min during early recovery from exercise, with plasma glucose determined immediately in duplicate with the glucose oxidase method using an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH). If the plasma glucose concentration was <70 mg/dL, then exercise was terminated (unless in the recovery period) and 20 g of oral dextrose tablets was administered. At $t = 70$ min, subjects received an insulin bolus using their individual insulin-to-carbohydrate ratio to cover a standardized meal containing 44–50 g of carbohydrate constituting ~55% of calories with ~20% calories from protein and ~25% from fat, with the meal ingested at $t = 75$ min and subsequent samples collected at $t = 90$, 105, 120, 135, and 165 min. A correction bolus was added to the carbohydrate bolus only if the premeal glucose concentration was ≥270 mg/dL.

Biochemical Analysis

Additional blood samples were collected at each time point on ice into tubes containing EDTA, and for peptide hormones, Protease Inhibitor Cocktail (Sigma-Aldrich, St. Louis, MO), centrifuged at 4°C, separated, and frozen at −80°C for subsequent analysis. Plasma glucagon and insulin levels were measured in duplicate by double antibody radioimmunoassays (Millipore, Billerica, MA). We have previously demonstrated that this insulin assay performs reliably in the presence of insulin autoantibodies, except in rare cases of extremely high-titer insulin autoantibodies where assay interference is readily apparent (18). The plasma lactate level was measured in duplicate using an automated lactate analyzer (YSI 2900; Yellow Springs Instruments). Plasma β-*O*-hydroxybutyrate and nonesterified fatty acid levels were measured in duplicate using enzymatic colorimetrics (Wako Chemicals, Richmond, VA). Samples from all four conditions in each subject were assayed simultaneously.

Statistical Analysis

The primary outcome was the plasma glucose level during exercise and early recovery. The MDG condition was compared with each of the conditions using a linear mixed model with repeated measures that accounts for the correlation due to the crossover design and the correlation due to multiple measures, adjusting for baseline glucose level and treatment period. In the event that exercise was terminated early because of a glucose concentration <70 mg/dL and the participant was treated for hypoglycemia (or if the participant was treated for hypoglycemia during early recovery [prior to the meal]), the nadir glucose value was carried forward through the end of early recovery. Prespecified secondary outcomes included the occurrence of hypoglycemia (plasma glucose <70 mg/dL) or hyperglycemia (plasma glucose ≥250 mg/dL) during exercise or early recovery (19) and CGM metrics during the late recovery period. The late recovery period was defined as the time from 90 min after ingestion of the standardized meal until 1200 h the next day. Nadir, peak, and mean glucose levels; coefficient of variation (CV); the percentage of time spent with glucose concentrations of <54, <70, >180, and >250 mg/dL were calculated from the CGM data, as well as the number of events with glucose concentrations of <54 and <70 mg/dL for at least 15 min. CV for glucose was calculated from the glucose SD divided by mean glucose.

Data are expressed as the mean ± SD or median (interquartile range [IQR]), unless otherwise stated. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). All *P* values are two-sided.

RESULTS

Between June 2016 and February 2017, 15 participants successfully completed all four exercise sessions and were included in the efficacy analyses, and 1 additional participant completed at least one exercise session and was included in the safety analyses (Supplementary Fig. 2). Among the 15 completers, 6 (40%) were female with a median age of 30 years (IQR 25–43 years), BMI of 24 kg/m^2 (23–27 kg/m^2), type 1 diabetes duration of 22 years (14–31 years), and HbA_{1c} of 6.8% (6.5–7.6%) (51 mmol/mol [48–60 mmol/mol]); 12 had an undetectable (<0.05 ng/mL) random C-peptide level that was 0.11, 0.20, and 0.45 ng/mL in the remaining 3 completers and a VO_{2max} of 42 mL/kg/min (35–51 mL/kg/min). The ancestry of 12 participants was non-Hispanic white, that of 2 was Hispanic or Latino, and that of 1 was Asian.

At baseline prior to the start of the exercise sessions, the plasma glucose concentration was similar across the conditions of control, insulin reduction, glucose tablets, and MDG (120 ± 16 vs. 119 ± 17 vs. 115 ± 13 vs. 118 ± 21 mg/dL). During exercise, plasma glucose concentrations decreased under control and insulin reduction and increased with glucose tablets and MDG ($P < 0.001$) (Fig. 1*A*) such that the plasma glucose concentration at the end

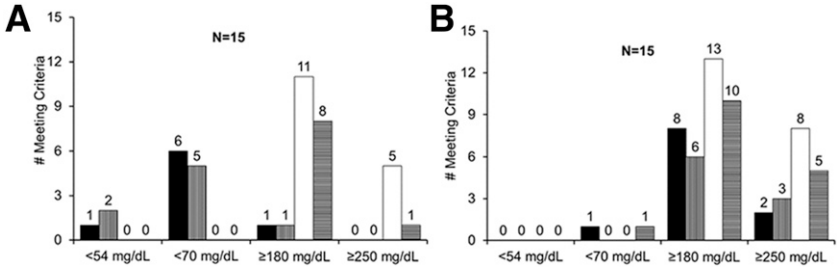

Figure 2—Occurrence of hypoglycemia and hyperglycemia under conditions of no intervention (control), basal insulin reduction, oral glucose tablets, or MDG administered 5 min prior to the start of exercise and assessed by plasma glucose during the 45 min of exercise and 30 min of early recovery (*A*) as well as for the subsequent 90 min after bolus insulin administration and ingestion of a standardized meal (*B*). Black bar represents control; vertical stripes represent insulin reduction; white bar represents glucose tabs; horizontal stripes represent MDG.

of exercise was 86 ± 30 vs. 85 ± 25 vs. 174 ± 59 vs. 161 ± 39 mg/dL and after early recovery was 90 ± 34 vs. 92 ± 34 vs. 222 ± 66 vs. 163 ± 49 mg/dL. Glucagon remained unchanged during exercise and early recovery under control, insulin reduction, and glucose tablet conditions and increased with MDG administration such that the plasma glucagon concentration 30-min postintervention was 55 ± 12 vs. 53 ± 9 vs. 61 ± 21 vs. 424 ± 201 pg/mL ($P < 0.001$) (Fig. 1*C*). Insulin levels were similar at baseline (24 ± 16 vs. 23 ± 10 vs. 25 ± 14 vs. 22 ± 13 μU/mL) and remained unchanged and not different across the four conditions during exercise and early recovery (Fig. 1*E*). After the standardized meal, plasma glucose levels converged and at 90-min postingestion were 178 ± 57 vs. 160 ± 67 vs. 209 ± 67 vs. 187 ± 71 mg/dL (Fig. 1*B*), whereas the glucagon concentration under the MDG condition returned to baseline (Fig. 1*D*) and insulin increased similarly

Table 1—CGM metrics during the exercise period and late recovery from exercise

	Control	Insulin reduction	Glucose tablets	MDG	*P* value
Exercise period¶	*N* = 12	*N* = 14	*N* = 14	*N* = 14	
Nadir glucose, mg/dL	75 (58–89)	87 (66–99)	120 (93–128)	128 (1,110–136)	<0.001
Peak glucose, mg/dL	121 (113–142)	146 (116–161)	197 (173–282)	171 (153–189)	<0.001
Mean glucose, mg/dL	95 (91–103)	106 (102–124)	162 (140–212)	155 (132–166)	<0.001
CV, %	14 (8–25)	16 (7–26)	17 (11–21)	11 (6–16)	0.25
Time <54 mg/dL, %	5 ± 10	1 ± 4	0 ± 0	0 ± 0	0.06
Time <70 mg/dL, %	12 ± 20	10 ± 17	0 ± 0	1 ± 4	0.02
Time 70–180 mg/dL, %	84 ± 22	89 ± 19	72 ± 33	80 ± 31	0.52
Time >180 mg/dL, %	4 ± 13	1 ± 4	28 ± 33	20 ± 32	0.007
Time >250 mg/dL, %	0 ± 0	0 ± 0	11 ± 17	5 ± 18	0.009
Hypo events <54 mg/dL, *n*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.43
Hypo events <70 mg/dL, *n*	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0.09
Entire late recovery period*	*N* = 14	*N* = 13	*N* = 13	*N* = 14	
Nadir glucose, mg/dL	45 (39–60)	44 (40–56)	49 (40–55)	51 (40–53)	0.99
Peak glucose, mg/dL	241 (216–279)	239 (222–299)	267 (211–331)	269 (235–281)	0.43
Mean glucose, mg/dL	129 (114–144)	139 (127–149)	130 (117–148)	147 (126–161)	0.16
CV, %	32 (29–42)	35 (33–40)	36 (32–42)	33 (31–35)	0.69
Time <54 mg/dL, %	3 ± 3	3 ± 3	3 ± 1	2 ± 2	0.67
Time <70 mg/dL, %	10 ± 9	8 ± 6	8 ± 6	6 ± 4	0.84
Time 70–180 mg/dL, %	73 ± 12	71 ± 10	69 ± 20	67 ± 15	0.63
Time >180 mg/dL, %	16 ± 13	21 ± 12	23 ± 20	26 ± 16	0.24
Time >250 mg/dL, %	1 ± 2	4 ± 9	9 ± 17	5 ± 7	0.26
Hypo events <54 mg/dL, *n*	1 (0–2)	1 (0–1)	0 (0–1)	0 (0–1)	0.61
Hypo events <70 mg/dL, *n*	2 (1–3)	2 (1–3)	2 (2–3)	2 (1–2)	0.91
Afternoon/evening recovery period€	*N* = 14	*N* = 13	*N* = 13	*N* = 14	
Nadir glucose, mg/dL	47 (39–60)	44 (40–56)	49 (40–55)	53 (40–62)	0.77
Peak glucose, mg/dL	223 (184–257)	222 (212–271)	245 (202–331)	253 (196–278)	0.36
Mean glucose, mg/dL	129 (95–146)	131 (108–146)	124 (117–135)	143 (115–171)	0.16
CV, %	32 (30–40)	35 (35–43)	40 (32–42)	33 (28–35)	0.56
Time <54 mg/dL, %	5 ± 6	5 ± 4	3 ± 3	2 ± 3	0.50
Time <70 mg/dL, %	14 ± 12	12 ± 8	11 ± 6	10 ± 8	0.77
Time 70–180 mg/dL, %	72 ± 15	70 ± 13	73 ± 12	69 ± 19	0.80
Time >180 mg/dL, %	14 ± 15	19 ± 16	16 ± 14	21 ± 18	0.61
Time >250 mg/dL, %	1 ± 2	5 ± 11	5 ± 9	6 ± 9	0.18
Hypo events <54 mg/dL, *n*	1 (0–2)	1 (0–1)	0 (0–1)	0 (0–1)	0.54
Hypo events <70 mg/dL, *n*	1 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	0.89
Overnight recovery period¥	*N* = 13	*N* = 13	*N* = 11	*N* = 13	
Nadir glucose, mg/dL	102 (83–109)	93 (74–117)	77 (68–165)	91 (76–107)	0.86
Peak glucose, mg/dL	174 (157–226)	201 (153–221)	186 (121–267)	209 (180–252)	0.64
Mean glucose, mg/dL	132 (119–154)	137 (115–168)	128 (100–205)	150 (141–180)	0.71
CV, %	15 (13–27)	13 (7–21)	15 (12–22)	21 (12–31)	0.45
Time <54 mg/dL, %	2 ± 5	1 ± 3	0 ± 0	2 ± 3	0.41
Time <70 mg/dL, %	5 ± 11	4 ± 3	3 ± 7	4 ± 8	0.99
Time 70–180 mg/dL, %	77 ± 29	66 ± 34	63 ± 41	60 ± 35	0.60
Time >180 mg/dL, %	18 ± 27	30 ± 35	34 ± 42	36 ± 34	0.53
Time >250 mg/dL, %	2 ± 5	5 ± 18	14 ± 31	5 ± 10	0.36
Hypo events <54 mg/dL, *n*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.57
Hypo events <70 mg/dL, *n*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.99

Continued on p. 1914

Table 1—Continued

	Control	Insulin reduction	Glucose tablets	MDG	*P* value
Morning recovery period£	*N* = 12	*N* = 13	*N* = 11	*N* = 14	
Nadir glucose, mg/dL	74 (57–92)	71 (62–95)	77 (63–88)	94 (87–113)	0.02
Peak glucose, mg/dL	195 (182–230)	196 (176–222)	199 (181–258)	221 (177–237)	0.99
Mean glucose, mg/dL	133 (121–152)	145 (130–163)	141 (121–152)	145 (130–166)	0.73
CV, %	30 (23–39)	26 (19–36)	28 (21–35)	25 (16–28)	0.26
Time <54 mg/dL, %	0 ± 1	2 ± 4	0 ± 1	0 ± 0	0.33
Time <70 mg/dL, %	10 ± 18	6 ± 9	3 ± 6	2 ± 4	0.11
Time 70–180 mg/dL, %	69 ± 27	75 ± 19	70 ± 31	70 ± 30	0.99
Time >180 mg/dL, %	21 ± 27	19 ± 18	27 ± 31	29 ± 31	0.86
Time >250 mg/dL, %	2 ± 5	3 ± 8	12 ± 29	2 ± 7	0.77
Hypo events <54 mg/dL, *n*	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.17
Hypo events <70 mg/dL, *n*	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0.34

Data are median (IQR) or mean ± SD, unless otherwise indicated. Hypo events are defined as at least 15 min below each cutoff. Hypo, hypoglycemic. ¶The exercise period was defined from the start of exercise until 75 min after to include the early recovery phase prior to standardized meal ingestion; included data were limited to periods with at least 30 min of CGM data. *The entire late recovery period was defined from 90 min after the standard meal until noon the day after each exercise session; included data were limited to periods with at least 12 h of CGM data. €The afternoon/evening period was defined from 90 min after the standard meal until 2400 h; included data were limited to periods with at least 6 h of CGM data. ¥The overnight period was defined from midnight to 0600 h the day after each exercise session; included data were limited to periods with at least 3 h of CGM data. £The morning period was defined from 0600 to 1200 h the data after each exercise session; included data were limited to periods with at least 3 h of CGM data.

across the four conditions after the meal bolus to 40 ± 20 vs. 40 ± 23 vs. 50 ± 39 vs. 36 ± 16 μU/mL by 90-min postingestion (Fig. 1*F*).

During the exercise and early recovery periods, six subjects experienced hypoglycemia (plasma glucose <70 mg/dL) during control, five during insulin reduction, and none with glucose tablets or MDG; five subjects experienced hyperglycemia (plasma glucose ≥250 mg/dL) with glucose tabs and one with MDG (Fig. 2*A*). During the 90 min after ingestion of the standardized meal, there was no difference in the occurrence of hypoglycemia or hyperglycemia across conditions (Fig. 2*B*).

During exercise, heart rate and perceived exertion were similar across all conditions. The percentage of peak heart rate across all time points and conditions was 69 ± 4.2%; the median perceived exertion was either 10 or 11 (i.e., deemed to be light exercise) at the 10-, 20-, and 30-min time points during all conditions. No participants reported nausea during exercise, but two participants reported nausea with symptoms of bloating after ingesting the postexercise meal for the MDG condition. Plasma lactate, β-*O*-hydroxybutyrate, and nonesterified fatty acid levels were similar across all conditions (Supplementary Fig. 3).

CGM measures during exercise and early recovery were consistent with the plasma glucose measures during the same period (Table 1). During the late recovery period assessed by CGM, there was no difference in any of the glycemic control metrics during the entire period or when assessed only in the afternoon/evening after exercise, during the overnight period, or the following morning (Table 1 and Fig. 3).

CONCLUSIONS

These results demonstrate that MDG (i.e., ~150 μg of glucagon) may be an effective strategy for the prevention of exercise-induced hypoglycemia in adults with type 1 diabetes. In addition, MDG may be more effective for preventing exercise-induced hypoglycemia than insulin reduction that was associated with a similar rate and magnitude of hypoglycemia as no intervention. Moreover, although MDG was as effective as glucose tablets for preventing exercise-induced hypoglycemia, MDG may result in less postintervention hyperglycemia than ingestion of carbohydrate and avoids the consumption of unnecessary calories.

Previous studies have shown that the increase in plasma glucagon levels that occurs in individuals without diabetes during exercise is absent in patients with type 1 diabetes (9). Although the current study did not include a group of individuals without type 1 diabetes, glucagon levels remained expectantly flat during exercise under conditions of no intervention, insulin reduction, and glucose tablets and increased briskly within 30 min of subcutaneous administration of MDG. The pharmacokinetic response to the 150-μg dose was almost identical to that reported in the dose-seeking study of the Xeris G-Pen Mini glucagon product (15), suggesting that exercise does not affect the rapid absorption of MDG from subcutaneous tissue. The peripherally measured glucagon concentrations are higher than those reported for individuals without diabetes during exercise (9); however, the peripheral rather than portal delivery of subcutaneously administered glucagon likely requires higher levels in the systemic circulation in order to oppose insulin action on the liver and increase endogenous glucose production during exercise.

Nausea without vomiting has been reported infrequently after exposure to 150 μg of MDG (0 of 12 [15] and 3 of 17 [16] participants in previous studies), which is consistent with complaints in 2 of the 15 participants here. Although this is likely related to the established effect of glucagon to relax gastrointestinal smooth muscle (20), nausea occurred more often with a 300-μg dose of MDG (4 of 12 participants) (15) and is observed with or without vomiting in more than a third of individuals treated with 1-mg emergency doses of glucagon (21). In the current study, the ~1 in 10 chance of experiencing nausea was related to ingestion of the standardized meal after exercise. Delaying subsequent meals may help those few individuals to avoid nausea associated with the use of MDG as observed in this study.

This study also adds to our understanding of the limitations of existing approaches for mitigating exercise-associated hypoglycemia. There are several approaches

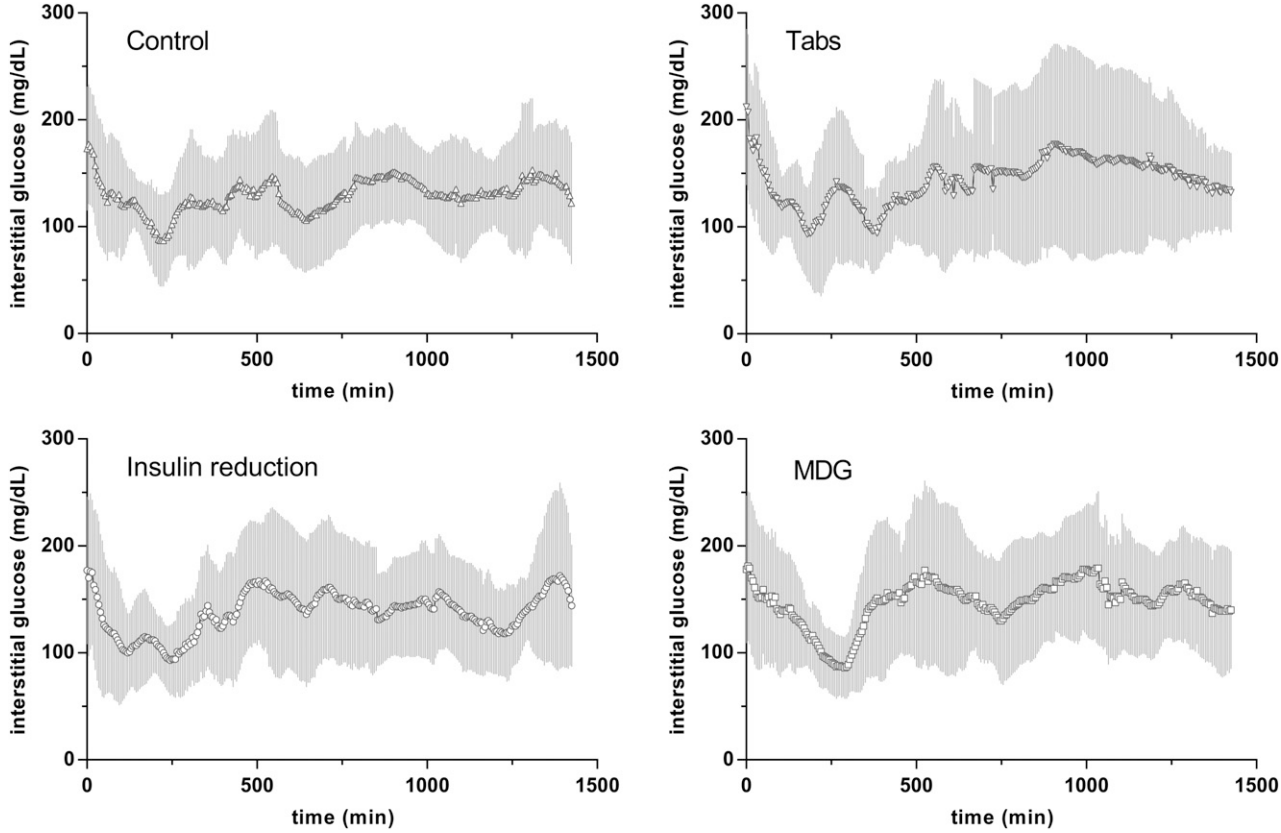

Figure 3—Interstitial glucose from CGM during late recovery, shown relative to the time elapsed since the start of the late recovery period (90 min after the standardized meal). Data are the mean ± SD.

to insulin reduction that have been tested in relation to aerobic exercise. In children with type 1 diabetes, stopping basal insulin during exercise was associated with less hypoglycemia than when it was continued but resulted in a greater frequency of postexercise hyperglycemia (12). In adults, reducing basal insulin by 80% may be more effective than a 50% reduction during moderate aerobic activity as was conducted here, but again may be associated with higher postexercise glucose concentrations (13). Reducing basal insulin delivery by 50% an hour prior to moderate aerobic exercise did not prevent the development of hypoglycemia and, similar to the data here, did not affect circulating concentrations of insulin (14). This may be related to an exercise-associated rise in insulin absorption rate at the site of insulin delivery. In line with this possibility, even if basal insulin suspension occurs at the time of exercise onset, insulin levels can rise in circulation once the exercise starts (13). We chose a 50% reduction in basal insulin delivery 5 min prior to exercise as this is commonly recommended in practice (22). This basal insulin reduction strategy near exercise onset had no effect in preventing exercise-induced hypoglycemia relative to no intervention, thus supporting a greater reduction (i.e., 80–100% basal rate reduction), perhaps well in advance of the activity, which has recently been recommended (23) but not yet formally tested.

Regarding the ingestion of oral carbohydrate as a strategy to prevent exercise-induced hypoglycemia, current recommendations range from ~0.3 to 1.0 g of carbohydrate per minute of aerobic exercise depending on the timing of the exercise relative to the last insulin administration (23). Under the condition of glucose tablets, we provided 20 g of carbohydrate in the form of dextrose tablets 5 min before the start of exercise and another 20 g after 30 min of exercise. Although this approach was effective for preventing exercise-induced hypoglycemia, it also led to significant development of postexercise hyperglycemia. After the first 20 g of oral glucose, the plasma glucose level rose modestly and quite similarly as the level after MDG administration during exercise but then increased further with the second administration of 20 g glucose orally. Unfortunately, we cannot know whether only 20 g of oral glucose 5 min before exercise would have been sufficient for preventing exercise-induced hypoglycemia throughout the completion of 45 min of exercise and through the early recovery period, but that dose may be the more appropriate comparator to MDG for future studies.

We did not observe a difference in glycemic control as measured by CGM during the late recovery period after exercise regardless of the strategy used to prevent exercise-associated hypoglycemia relative to the control strategy of no intervention. We may have been limited in our ability to detect a difference by the carefully controlled conditions of the exercise sessions and subsequent standardized meals and activity restrictions that may have prevented significant postexercise variability in glucose control. In particular, the exercise sessions were conducted in the morning under fasting conditions in order to minimize confounding effects from variable nutrient ingestion and insulin administration present before late-day exercise, and late day exercise carries a greater risk for the development of subsequent late-onset hypoglycemia (24). Future studies involving more "real-life" and less controlled activity will be important to determine

whether MDG is as effective in minimizing the risk for "late" exercise-associated hypoglycemia as it appears to be for preventing "early" exercise-induced hypoglycemia. Another limitation is that we did not include patients using multiple daily injections for insulin delivery who may be at even greater risk for exercise-associated hypoglycemia (25) and require inclusion in future studies.

In conclusion, MDG may be more effective than insulin dose reduction for preventing exercise-induced hypoglycemia and may result in less postintervention hyperglycemia than the ingestion of carbohydrate. Because many variations for insulin dose reduction and carbohydrate ingestion prior to exercise exist, it is likely that a strategy not tested in the current study may result in comparable glucose control during exercise as that reported here for MDG. Because MDG is administered at the time of exercise and avoids the additional caloric intake that occurs with the ingestion of carbohydrate, individuals with type 1 diabetes may find that this approach helps to facilitate engagement in aerobic exercise through the stabilization of glucose levels and also assists with the achievement of body weight goals. Future long-term studies of MDG intervention for exercise in individuals with type 1 diabetes are warranted.

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