



Home Use of Mini-Dose Glucagon As a Novel Treatment for Hypoglycemia Following Repeated, Prolonged Fasts in Type 1 Diabetes During Ramadan

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OBJECTIVE

We determined the efficacy of self-administered subcutaneous mini-dose glucagon (MDG) to treat fasting-induced hypoglycemia in type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

This was a 4-week randomized, controlled crossover trial of 2-week MDG or 2-week oral glucose tablets (OG, control) involving 17 adults with T1D during Ramadan.

RESULTS

Compared with OG, MDG demonstrated a significant higher change in blood glucose from baseline to 30 min (Δ^{t30} , $P < 0.001$) and 1 h (Δ^{t60} , $P = 0.02$). The efficacy of MDG was preserved following ≥ 8 h fasting with significantly higher Δ^{t30} in MDG ($P = 0.01$). Over the entire 2 weeks, MDG period had increased time in 70–180 mg/dL ($P = 0.009$) and less time < 70 mg/dL ($P = 0.04$). MDG use resulted in higher completion of fasts compared with OG ($P < 0.001$).

CONCLUSIONS

MDG administration is an effective alternative to OG for prevention and treatment of fasting-induced hypoglycemia, offering improved glycemic control and promoting successful completion of prolonged fasts.

Certain situations, such as physical activity and fasting, can significantly increase the risk of hypoglycemia in type 1 diabetes (T1D) (1,2). Fasting is part of several religious practices, and intermittent fasting is also commonly practiced given the potential metabolic benefits (3).

Given the known potential for glycemic derangements with intensively managed T1D in general, as well as higher risks of hypoglycemia from observational data, most international guidelines on diabetes and Ramadan consider T1D as a “high-risk” situation where fasting is not recommended (1,4). However despite recommendations and alternatives, $>40\%$ of adult Muslims with T1D continue fasting in Ramadan as they feel it is essential to their spiritual practice, which presents a challenge for health care professionals (5). Advances in therapies and technologies

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have provided avenues to consider safer fasting practices in T1D; nevertheless, the risks from hypoglycemia still need to be addressed (6).

Having been studied in children and exercise as a subcutaneous treatment to manage hypoglycemia, mini-dose glucagon (MDG) is now an accepted treatment for hypoglycemia in certain limited situations (7,8). Unlike oral medications, subcutaneous injections do not invalidate Ramadan fasts (9). While MDG use could be considered in Ramadan to avoid or treat hypoglycemia without having to break the fast and avoid psychological implications of doing so, its use in the context of prolonged fasts remains untested. This is of special concern during fasting given glycogen store depletion and altered glycogen synthesis in T1D (10,11). This study aimed to understand whether self-administered MDG is safe and effective in preventing or treating mild and moderate hypoglycemia in people with T1D in home settings who performed consecutive, prolonged fasts during Ramadan.

RESEARCH DESIGN AND METHODS

This was a 4-week prospective, randomized, controlled crossover trial recruiting adults aged 18–65 years, with T1D diagnosed for >2 years and HbA_{1c} <8.5% (69 mmol/mol), who chose to fast during Ramadan (fasting time window = ~15 h). The protocol is listed on ClinicalTrials.gov (NCT03970772) and was approved by the National Committee of Bioethics (1440-1676406). All participants received real-time continuous glucose monitoring (rt-CGM) (Dexcom G5; Dexcom, San Diego, CA) and were randomized (unblinded) to 2-week MDG or 2-week oral glucose tablets (OG, control) to treat fasting-induced hypoglycemia, with a crossover thereafter.

Recruited participants were instructed to check their blood glucose with the study meter (OneTouch Verio; LifeScan, Milpitas, CA) if they developed hypoglycemia symptoms, their rt-CGM device gave a reading <70 mg/dL or rt-CGM glucose <100 mg/dL with downward arrow, and they intended to treat to prevent hypoglycemia. Participants were trained to reconstitute glucagon (GlucaGen Hypokit, Novo Nordisk) with sterile water to a concentration of 1 mg/mL just prior to each dose and then inject subcutaneously using a standard U-100

insulin syringe according to the study protocol (Supplementary Fig. 4). When the blood glucose was 50–69 mg/dL, treatment was 150 µg of MDG or 15 g of OG (depending on study period), and when the blood glucose was 40–49 mg/dL, treatment was doubled (300 µg of MDG or 30 g of OG). MDG dosage was defined based on previous literature, and the OG dosage was defined according to American Diabetes Association clinical practice guideline (2,12). Hypoglycemia events were analyzed if they met the study testing and treatment protocol (Supplementary Fig. 3).

The primary outcome was the change from baseline to 30 min in blood glucose values (Δ^{t30}). Secondary end points are listed in Table 1. Statistical rt-CGM metrics comparisons were analyzed using multilevel (mixed) regression models with repeated measures that accounts for the correlation due to the crossover design and multiple measures. Subgroup analysis was carried out to evaluate the effect of prolonged fasting.

RESULTS

There were 17 participants and 80 hypoglycemia episodes that met the criteria for analysis in the crossover trials (Supplementary Fig. 1 and Supplementary Table 1).

The primary end point Δ^{t30} and secondary end point Δ^{t60} were significantly higher for MDG compared with OG (65.3 ± 26.5 vs. 44.3 ± 20.1 [$P < 0.001$] and 74.5 ± 50.1 vs. 46.4 ± 26.3 mg/dL [$P < 0.02$], respectively) (Table 1). Further subanalysis revealed significantly increased Δ^{t30} for MDG compared with OG for hypoglycemic events that occurred after 8 h of fasting (60.8 ± 22.1 vs. 41.5 ± 16.7 mg/dL; $P = 0.01$) (Supplementary Table 2).

MDG users had significantly higher mean glucose 1 and 2 h after hypoglycemic events (80.5 ± 27.9 vs. 68.1 ± 18.7 [$P = 0.04$] and 106.2 ± 37.7 vs. 87.3 ± 21.7 mg/dL [$P = 0.03$], respectively) and maximum rt-CGM glucose (114.4 ± 44.5 vs. 93.5 ± 29.3 [$P = 0.03$] and 143.4 ± 55.4 vs. 120.4 ± 40.6 mg/dL [$P = 0.08$], respectively) compared with OG. The rt-CGM glucose concentrations for 82.9% MDG events and 50% OG events were ≥100 mg/dL or increased by ≥30 mg/dL within 1 h following treatment ($P = 0.01$). The rt-CGM data

for the entire 2-week MDG period demonstrated significantly increased time in range between 70 and 180 mg/dL (61.0% ± 10.3% vs. 55.1% ± 13.8%; $P = 0.009$) and less time <70 mg/dL (9.2% ± 5.8% vs. 12.8% ± 12.8%; $P = 0.04$). Other rt-CGM metrics were favorable for MDG but did not reach statistical significance (Table 1).

Participants with MDG showed a significant increase in completion of fasts compared with those given OG (100% vs. 88%; $P < 0.001$). Four events (16%) of analyzable hypoglycemic episodes required repeated dosages during the OG period compared with no events during the MDG period ($P = 0.01$), and success criteria were met for all seven preventable events during the MDG period (Table 1). In all cases after MDG, an acceptable glucose response occurred with no participant requiring any repeat dose within the time period of 4 h of the previous dose (Supplementary Fig. 2). Within the first hour, mean glucose at 15, 30, 45, 60 and 120 min was higher using MDG compared with OG (Supplementary Fig. 3).

Nausea and injection site discomfort were reported in 6 of 17 participants (intolerable nausea for 1 participant), and no serious adverse events were reported.

CONCLUSIONS

Our data demonstrate that using glucagon provides an effective alternative to oral options for treating fasting-induced hypoglycemia in the home setting for adults with T1D during Ramadan. An earlier and higher glycaemic response was observed with MDG over OG (Table 1 and Supplementary Fig. 3). This approach allowed completion of more fasts successfully. It builds on previous work and presents MDG (i.e., 150 µg of glucagon) as an effective treatment for hypoglycemia that can be applied to other prolonged, repetitive fasting situations such as nocturnal hypoglycemia, intermittent fasting, or exercising in the fasted state in T1D (2,8).

The pharmacokinetic response to the 150-µg dose showed an almost identical response to previous studies (2,13). This suggests that the rapid absorption and efficacy of MDG from subcutaneous tissue is not affected by prolonged, repetitive fasting. Data from fasting 8 h and no requirement for repeated treatments

Table 1—Comparison of study outcomes by treatment arm

Outcome	OG n = 25	MDG n = 40	Difference* Mean (95% CI)	P value
Comparison of study outcomes 1 and 2 h after hypoglycemic events				
Change in glucose at				
Time 0–15 min,† mg/dL‡	29.0 ± 22.7	37.4 ± 18.8	8.8 (–1.1, 18.8)	0.08
Time 0–30 min, mg/dL, Δ ^{t30} ‡	44.3 ± 20.1	65.3 ± 26.5	22.4 (10.6, 34.1)	<0.001
Time 0–45 min, mg/dL	46.4 ± 24.6	64.4 ± 48.5	16.9 (–2.4, 36.3)	0.09
Time 0–60 min, mg/dL, Δ ^{t60}	46.4 ± 26.3	74.5 ± 50.1	24.7 (3.3, 46.2)	0.02
Time 0–120 min, mg/dL	39.2 ± 34.4	60.6 ± 40.6	19.6 (–2.0, 41.1)	0.08
Minimum glucose in 60 min, mg/dL	53.7 ± 11.5	54.7 ± 11.5	1.2 (–3.2, 5.7)	0.58
Maximum glucose in 60 min, mg/dL	93.5 ± 29.3	114.4 ± 44.5	22.0 (2.0, 41.9)	0.03
Mean glucose in 60 min, mg/dL	68.1 ± 18.7	80.5 ± 27.9	12.5 (0.8, 24.1)	0.04
Time >180 mg/dL in 60 min, %	0 ± 0	3.22 ± 12.65	—	0.52
Time 70–180 mg/dL in 60 min, %	36.9 ± 33.6	43.3 ± 28.9	8.6 (–4.9, 22.2)	0.21
Time <70 mg/dL in 60 min, %	63.1 ± 33.6	53.9 ± 31.2	–10.3 (–24.0, 3.4)	0.14
Minimum glucose in 120 min, mg/dL	55.5 ± 12.5	54.9 ± 11.7	–0.8 (–5.8, 4.2)	0.75
Maximum glucose in 120 min, mg/dL	120.4 ± 40.6	143.4 ± 55.4	22.1 (–2.9, 47.1)	0.08
Mean glucose in 120 min, mg/dL	87.3 ± 21.7	106.2 ± 37.7	18.2 (2.3, 34.1)	0.03
Time >180 mg/dL in 120 min, %	4.23 ± 11.81	5.35 ± 16.31	2.03 (1.41, 2.65)	0.75
Time 70–180 mg/dL in 120 min, %	63.4 ± 19.0	56.1 ± 24.3	–5.1 (–16.6, 6.4)	0.39
Time <70 mg/dL in 120 min, %	33.0 ± 19.3	31.5 ± 22.7	–2.5 (–11.2, 6.1)	0.57
Glucose ≥100 mg/dL or increased by 30 mg/dL 1 h after treatment, n (%)§	11 (50.0)	29 (82.9)	7.02 (1.52, 32.4)	0.01
Treatment success from the first dose, n (%)¶	25 (84)	44 (100)	2.7 (1.6, 6.2)	0.01
Comparison of study outcomes over the entire 2 weeks of each treatment period				
Mean glucose, mg/dL	160.6 ± 29.1	154.2 ± 24.5	–2.1 (–10.1, 5.8)	0.60
Time >250 mg/dL, %	13.8 ± 10.4	10.7 ± 6.7	–2.2 (–6.1, 1.6)	0.26
Time >180 mg/dL, %	35.9 ± 16.0	31.2 ± 13.8	–3.2 (–6.7, 0.3)	0.07
Time 70–180 mg/dL, %	55.1 ± 13.8	61.0 ± 10.3	6.5 (1.7, 11.4)	0.009
Time <70 mg/dL, %	12.8 ± 12.8	9.2 ± 5.8	–6.0 (–11.6, –0.3)	0.04
Coefficient of variation, %	43.7 ± 79	42.4 ± 4.3	–2.5 (–6.4, 1.3)	0.20
Time where rt-CGM is active, %	93.5 ± 4.7	95.4 ± 3.7	–2.2 (–6.6, 1.4)	0.23
Completion of fasts, n (%) of days	192 (88)	219 (100)	2.6 (2.2, 6.7)	<0.001

Data are presented as mean ± SD unless indicated otherwise. *Differences reported as values for MDG minus values for OG. †Time point was set as “Time 0” when the participant experienced hypoglycemia. ‡Data derived from blood glucose meter. §Differences reported as values for MDG relative to values for OG. ||Glucose ≥50 mg/dL at 15 min and ≥70 mg/dL at 30 min after treatment, n (%).

further supports this (Table 1 and Supplementary Table 2).

Most participants reported a tolerable level of nausea, although slightly higher than previous reports. Further advancements in the development of a reusable pen (such as dasiglucagon) could reduce the relative discomfort associated with injections. Inhaled glucagon may provide an alternative approach, but can cause local adverse effects (14).

Participants in this study are representative of an average clinical cohort in Middle East and international clinics given their demographics and nonavailability of structured education programs. Limitations of this study include sample size, given constraints from the cost and challenge of performing larger clinical studies during Ramadan, and potential for selection bias given the use of CGM technologies.

To conclude, glucagon administration is an effective alternative to OG as for the

treatment and prevention of hypoglycemia following prolonged fasts in home settings. As newer ways of delivering and administering glucagon are developed, including dual-hormone closed-loop systems, this study provides rationale and validity for the use of glucagon in managing hypoglycemia in semifasted and fasted states in T1D (15).

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References

1. Salti I, Bénard E, Detournay B, et al. EPIDIAR study group. A population-based study of dia-

- betes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004;27:2306–2311
2. Rickels MR, DuBose SN, Toschi E, et al. T1D Exchange Mini-Dose Glucagon Exercise Study Group. Mini-dose glucagon as a novel approach to prevent exercise-induced hypoglycemia in type 1 diabetes. *Diabetes Care* 2018;41:1909–1916
3. Hoddy KK, Marlatt KL, Çetinkaya H, Ravussin E. Intermittent fasting and metabolic health: from religious fast to time-restricted feeding. *Obesity (Silver Spring)* 2020;28(Suppl. 1):S29–S37
4. International Diabetes Federation and DAR International Alliance. *Diabetes and Ramadan: Practical Guidelines*, Brussels, Belgium: International Diabetes Federation, 2021. Accessed 4 April 2021. Available from www.idf.org/guidelines/diabetes-in-ramadan and www.daralliance.org
5. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2013;369:362–372
6. Hussain S, Choudhary P, Hopkins D. Type 1 diabetes and fasting in Ramadan: time to rethink classification of risk? *Lancet Diabetes Endocrinol* 2020;8:656–658
7. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*. *Can J Diabetes* 2018;42(Suppl. 1):S1–S325
8. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001;24:643–645
9. Aadil N, Houti IE, Moussamih S. Drug intake during Ramadan. *BMJ* 2004;329:778–782
10. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. *Nat Rev Neurosci* 2018;19:63–80
11. Hwang JH, Perseghin G, Rothman DL, et al. Impaired net hepatic glycogen synthesis in insulin-dependent diabetic subjects during mixed meal ingestion. A ^{13}C nuclear magnetic resonance spectroscopy study. *J Clin Invest* 1995;95:783–787
12. American Diabetes Association. 6. Glycemic Targets: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care* 2021;44(Suppl. 1):S73–S84
13. Haymond MW, DuBose SN, Rickels MR, et al.; T1D Exchange Mini-dose Glucagon Study Group. Efficacy and safety of mini-dose glucagon for treatment of nonsevere hypoglycemia in adults with type 1 diabetes. *J Clin Endocrinol Metab* 2017;102:2994–3001
14. Sherr JL, Ruedy KJ, Foster NC, et al.; T1D Exchange Intranasal Glucagon Investigators. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. *Diabetes Care* 2016;39:555–562
15. Beato-Vibora PI, Arroyo-Díez FJ. New uses and formulations of glucagon for hypoglycaemia. *Drugs Context* 2019;8:212599