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A Case Report of Diabetic Ketoacidosis With Combined Use of a Sodium Glucose Transporter 2 Inhibitor and Hybrid Closed-Loop Insulin Delivery

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artificial intelligence, closed loop insulin delivery, diabetic ketoacidosis, insulin pump, type 1 diabetes mellitus, sodium glucose transporter 2 (SGLT-2) inhibitor

Since the approval of sodium glucose transporter 2 (SGLT-2) inhibitors, case reports have described euglycemic diabetic ketoacidosis (eDKA).[1-3] When used off-label in people with type 1 diabetes, eDKA may result when patients fail to administer extra insulin in response to an acute precipitant.[4] The introduction of the first hybrid closed-loop insulin delivery system—MiniMed 670G—allows insulin pump users with type 1 diabetes to receive automatically-adjusting basal insulin delivery. We report a case of a woman with type 1 diabetes using an SGLT-2 inhibitor who presented with eDKA after starting hybrid closed-loop insulin delivery.

A 54-year-old woman, with a 15-year history of type 1 diabetes, presented to the emergency department (ED) with one day of vomiting and confusion. She did not attribute her symptoms to diabetes, noting blood glucoses in the low 200 mg/dl (11.1 mmol/L) range. She had over 10 years' experience using Medtronic insulin pumps. One year before this event, she was started on empagliflozin (300 mg/day). Four weeks before presentation, she was started on MiniMed 670G, and two weeks later, auto mode was initiated. Upon ED presentation, laboratory evaluation showed sodium 143 mmol/L, potassium 5 mmol/L, chloride 107 mmol/L, bicarbonate <5 mmol/L, BUN >30 mg/dL, creatinine 1.36 mg/dL, glucose 519 mg/dL (28.8 mmol/L), anion gap 30, eGFR 44 mL/min, beta-hydroxybutarate 12.09 mmol/L (reference 0.02-0.27 mmol/L), venous pH 6.90, urine ketones >80 mg/dL, and urine glucose >500 mg/dL. We removed her insulin pump and found the infusion cannula was kinked. She was started on our hospital's intravenous insulin DKA protocol. Within 10 hours, her symptoms resolved and her anion gap closed. She resumed using her pump and was discharged home with the empagliflozin discontinued.

We analyzed her pump data (see Table 1). While in manual mode and on empagliflozin, she averaged 10 units bolus and 17 units basal insulin daily. In the first 12 days after entering auto mode, daily bolus insulin remained similar at 11 units, while auto mode decreased basal insulin to 12 units. On the morning her symptoms began, she changed her infusion set. Fingerstick glucose readings the day of admission correlated with her sensor, ranging from 150-225 mg/dL (8.3-12.5 mmol/L) and did not increase until she came to the ED. Auto mode basal insulin increased from 0.9 units/hr to 1.2 units/hr, where it remained for the 6 hours prior to admission. Three weeks after discharge and discontinuation of empagliflozin, her average daily basal insulin total in auto mode had increased by 60%, to 20 units daily.

While, as with many cases, the exact cause of DKA is unknown, this patient had multiple likely contributors. First, her infusion cannula was kinked. Second, the auto mode algorithm had significantly decreased her basal rates from her previous manual mode doses (see Table 1), which we hypothesize may have been due to use of an SGLT-2 inhibitor. Third, the SGLT-2 inhibitor inhibited the hyperglycemia that typically would have resulted from her kinked cannula and been a warning sign. Fourth, there is a tendency in some patients using SGLT-2 inhibitors for increased ketone production. Finally, this well-educated patient did not intervene to check ketones, change her infusion set, or inject insulin via syringe.

This case is the first to our knowledge where a patient may have presented in DKA as a result of the combined effects of an SGLT-2 inhibitor and hybrid closed-loop insulin delivery. This case provides several lessons. Just like airline pilots, patients must be alert to the risks of "automation complacency," where a human operator monitoring an automated system enters a

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Table 1. Average Glucose Levels and Insulin Use Before and After SGLT-2 Inhibitor Use in Hybrid Closed-Loop Insulin Delivery.

Time period (relative to hospital admission day 0)	SGLT-2 inhibitor used?	Total daily insulin dose (units)	Bolus insulin amount (units)	Basal insulin amount (units)	% time in auto mode	Avg sensor glucose (mg/dL)	Sensor glucose std dev	Carbs per day (grams)
Day –28 to day –14 (manual mode)	Yes	27	10	17	0	148	50	111
Day –14 to day –3 (auto mode)	Yes	23	11	12	94	153	48	113
Day –3 to day 0 (auto mode)	Yes	23	10	13	82	178	48	98
Day 21 to day 35 (auto mode)	No	38	18	20	94	157	55	138

state of decreased vigilance and reduced monitoring frequency based on an assumed satisfactory system state.[5] Patients and physicians using hybrid closed-loop insulin delivery, as with any insulin pump, must remain vigilant about the risks of DKA. Although there is interest in the potential use of SGLT-2 inhibitors in patients with type 1 diabetes, until further study is done,[6] we suggest that extreme caution is warranted in any patient using hybrid closed-loop insulin delivery.

Abbreviations

DKA, diabetic ketoacidosis; ED, emergency department; eDKA, euglycemic diabetic ketoacidosis; SGLT-2, sodium glucose transporter 2.

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References

1. Rawla P, Vellipuram AR, Bandaru SS, Pradeep Raj J. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. *Endocrinol Diabetes Metab Case Rep*. 2017;1.
2. Chen J, Fan F, Wang JY, et al. The efficacy and safety of SGLT2 inhibitors for adjunctive treatment of type 1 diabetes: a systematic review and meta-analysis. *Sci Rep*. 2017;7:44128.
3. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab*. 2015;100:2849-2852.
4. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38:1687-1693.
5. Parasuraman R, Manzey DH. Complacency and bias in human use of automation: an attentional integration. *Hum Factors*. 2010;52:381-410.
6. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. *Diabetes Care*. Epub ahead of print 6 February 2019. DOI:10.2337/dc18-2316