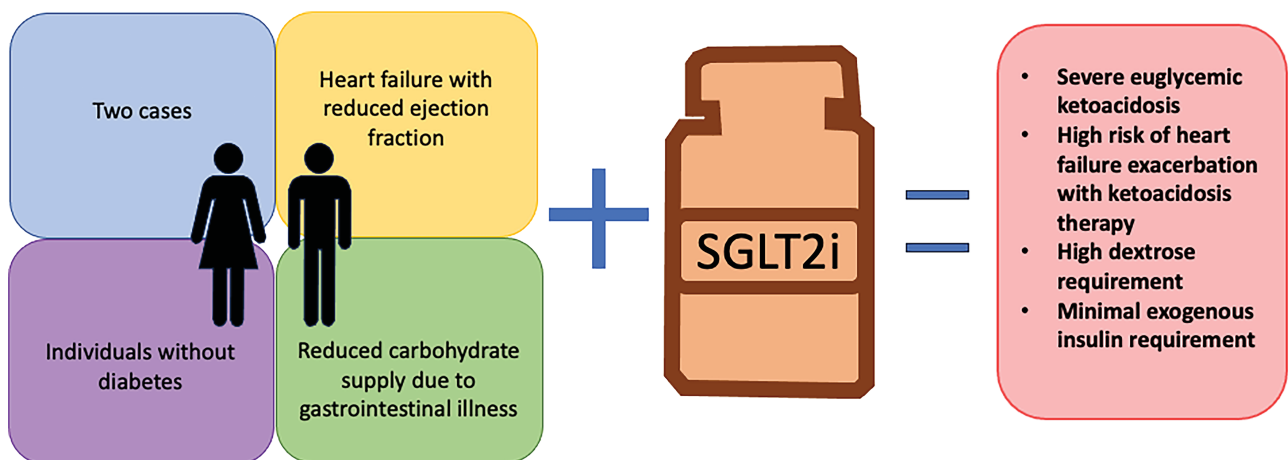


Euglycemic Ketoacidosis in Two Patients Without Diabetes After Introduction of Sodium–Glucose Cotransporter 2 Inhibitor for Heart Failure With Reduced Ejection Fraction

Mahesh M. Umapathysivam, James Gunton, Steve N. Stranks, and David Jesudason

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Two Case Reports of Euglycemic Ketoacidosis in Individuals Without Diabetes Treated With SGLT2i For Heart Failure



ARTICLE HIGHLIGHTS

• **Why did we undertake this study?**

This study was undertaken to demonstrate that euglycemic ketoacidosis due to sodium–glucose cotransporter 2 inhibitors (SGLT2i) can occur in individuals without diabetes and to describe the clinical features of this phenomenon.

• **What is the specific question(s) we wanted to answer?**

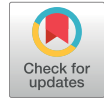
We aimed to describe the presentation and response to management of SGLT2i-associated ketoacidosis in individuals without diabetes with a focus on fluid and insulin management.

• **What did we find?**

High rates of intravenous dextrose may be required to support insulin infusion, and promotion of endogenous insulin secretion with dextrose can improve ketosis without exogenous insulin administration. Fluid resuscitation of SGLT2i-associated ketoacidosis in individuals without diabetes must consider the potential to exacerbate underlying heart failure.

• **What are the implications of our findings?**

SGLT2i-associated ketoacidosis can occur in individuals without diabetes, and such people may require more dextrose than individuals with diabetes. Fluid resuscitation must take into account the risk of exacerbating underlying heart failure.



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Mahesh M. Umapathysivam,^{1,2,3,4}
James Gunton,^{5,6} Steve N. Stranks,^{1,5} and
David Jesudason^{2,3,4}

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OBJECTIVE

Ketoacidosis induced by sodium–glucose cotransporter 2 inhibitor (SGLT2i) treatment has been consistently observed in clinical practice in patients with type 2 diabetes despite minimal indication from the landmark cardiovascular outcome trials. It has been postulated that individuals without diabetes will not develop this complication due to an adequate insulin secretory capacity, which will protect against significant ketone formation. Cardiovascular outcome trials examining SGLT2i use in individuals with heart failure but not diabetes have not reported ketoacidosis.

RESEARCH DESIGN AND METHODS

We describe the first two case reports of severe nondiabetic ketoacidosis after initiation of an SGLT2i for the treatment of heart failure with reduced ejection fraction, and we describe the management strategies employed and implication for the pathophysiology of SGLT2i-associated ketoacidosis.

RESULTS

Each individual presented with ketoacidosis triggered by reduced oral nutrition intake. For both individuals, ketoacidosis resolved with intravenous glucose administration, encouragement of consumption of oral glucose-containing fluid, and minimal insulin administration.

CONCLUSIONS

These two cases demonstrate that SGLT2i-associated ketoacidosis is possible in individuals without diabetes.

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are now widely used in individuals with type 2 diabetes. Consensus guidelines advocate the early use of SGLT2i to reduce progression of cardiovascular and renal diseases (1). As SGLT2i use has increased, so have rates of adverse effects. Real-world data suggest SGLT2i-associated ketoacidosis occurs at a rate of 1.8–4.9 cases per 1,000 patients (2,3). Importantly, the phenomenon of ketoacidosis was not appreciated in the initial randomized controlled trials of SGLT2i therapy in diabetes (4,5). The initial indication of the phenomenon was

¹Southern Adelaide Diabetes and Endocrine Services, Flinders Medical Centre, Adelaide, South Australia, Australia

²Endocrine Department, Queen Elizabeth Hospital, Woodville South, South Australia, Australia

³University of Adelaide, Adelaide, South Australia, Australia

⁴Basil Hetzel Institute, Woodville South, South Australia, Australia

⁵Flinders University, Adelaide, South Australia, Australia

⁶Department of Cardiovascular Medicine, Flinders Medical Centre, Adelaide, South Australia, Australia

Corresponding author: Mahesh M. Umapathysivam, mahesh.umapathysivam@sa.gov.au

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identified via case reports on off-label use of SGLT2i in type 1 diabetes and later on-label use in type 2 diabetes (2,3,6–8).

Landmark trials of SGLT2i in patients with heart failure without diabetes demonstrated clear benefit without evidence of ketoacidosis, and their use has been incorporated into society guidelines (5,9–11). It remains unclear whether individuals with normoglycemia and presumably normal insulin secretory capacity would be at risk for ketoacidosis.

Supporting the argument that a secretory deficit contributes to ketoacidosis risk is the observation of increased risk associated with elevated HbA_{1c} and the increased risk seen in individuals with type 1 diabetes (7,12). Conversely, SGLT2i-associated ketoacidosis may be driven by a reduction in blood glucose and subsequent reduction in the stimulus for insulin secretion rather than an absolute insulin deficit. To date, one case of mild SGLT2i-associated ketoacidosis has been reported in the perioperative period in a patient without diabetes (13).

Here, we describe two cases of severe ketoacidosis in patients without diabetes taking SGLT2i.

RESEARCH DESIGN AND METHODS

Case 1

A 28-year-old male individual with Duchenne muscular dystrophy and associated heart failure with reduced ejection fraction (HFrEF) (34%) was commenced on dapagliflozin 10 mg. Treatment was augmented with a combination of sacubitril 49 mg and valsartan 51 mg twice daily, spironolactone 25 mg daily, bisoprolol 7.5 mg daily, and prednisolone 15 mg daily. His HbA_{1c} prior to initiation of dapagliflozin was 33 mmol/mol (5.2%). Five months later, he presented with a 3- to 4-day history of reduced oral intake in the setting of gastritis triggered by a course of nonsteroidal anti-inflammatory medication for back pain. Over the 2 days prior he had progressive vomiting. He was unable to take his medication (including his dapagliflozin) for the 36 h preceding presentation. Admission blood tests revealed severe ketoacidosis (normal range included in parentheses): bicarbonate 9 mmol/L (22–32 mmol/L), ketones 5.2 mmol/L (<0.6 mmol/L), pH 7.14, plasma glucose (PG) 70.2 mg/dL (3.9 mmol/L), and anion gap 25 mmol/L (7–17 mmol/L). HbA_{1c} at presentation was 33 mmol/mol (5.2%).

Other causes of high-anion-gap acidosis were excluded. He had normal lactate (1.2 mmol/L [0.2–2.0 mmol/L]) and no history of ethanol use. There was no evidence of acute kidney injury (creatinine 0.1 [0.67–1.24 mg/dL]). He had adequate insulin secretory capacity (C-peptide 2,445 pmol/L, PG 138.6 mg/dL [7.7 mmol/L]); this was assessed while he received intravenous (i.v.) dextrose. He was managed with insulin-dextrose infusion; however, only 22.5 units of insulin were administered in the initial 24 h. Insulin was not administered for the first 12 h of his resuscitation due to hypoglycemia. Despite being treated with only i.v. dextrose for 12 h, his ketone concentration fell from 5.1 mmol/L to 2.4 mmol/L by the time of commencement of insulin infusion (Fig. 1). This likely reflects endogenous insulin secretion. Of note, despite 36 h without taking SGLT2i, he still had glucosuria, suggesting ongoing SGLT2i action. Ketoacidosis resolved in 48 h. Type 1 antibodies were undetectable. Dapagliflozin was not restarted.

Case 2

A 62-year-old female individual with a new diagnosis of HFrEF (34%) was commenced on perindopril 5 mg daily (switched to sacubitril-valsartan twice daily at 2 weeks, with each dose containing sacubitril 49 mg and valsartan 51 mg), rosuvastatin 5 mg daily, nebivolol 1.25 mg (increased to 2.5 mg at 2 weeks), and empagliflozin 10 mg. No glycated hemoglobin data were available. Prior to starting empagliflozin, nonfasting glucose was 77.4 mg/dL (4.3 mmol/L), within the normal range even for a fasting sample (<100 mg/dL [5.6 mmol/L]). Her medical history was significant for systemic lupus erythematosus (treated with hydroxychloroquine and low-dose prednisolone) and chronic obstructive pulmonary disease. She had no history of diabetes.

Six weeks after commencing empagliflozin, she presented to hospital with confusion, dysarthria, and severe metabolic acidosis. This presentation followed 1 week of reduced oral intake (25% of usual diet) and a mild diarrheal illness that resolved prior to presentation. She continued to take her usual medications, including empagliflozin.

Initial assessment revealed hemodynamic instability requiring inotropic support and a severe metabolic acidosis with pH 6.99 and bicarbonate 6 mmol/L (22–32 mmol/L). The

anion gap was 29 mmol/L (7–17 mmol/L), lactate 0.9 mmol/L (0.2–2.0 mmol/L), P_{CO}₂ 26 mmHg (35–45 mmHg), PG 4.3 mmol/L (77.4 mg/dL), capillary ketones 4.2 mmol/L (<0.6 mmol/L), β-hydroxybutyrate 1.61 mmol/L (<0.29 mmol/L), and acetoacetate 1.38 mmol/L (<0.09 mmol/L). HbA_{1c} was 44 mmol/mol (6.2%) which is in the prediabetes range. Type 1 diabetes antibodies were undetectable. C-peptide was measured during initial resuscitation with dextrose and demonstrated adequate insulin secretion, 1,972 pmol/L (366–1,466 pmol/L) (paired glucose concentration 77.4 mg/dL [4.3 mmol/L]). Glucagon concentration was elevated at 290 pg/mL (<208 pg/mL). She had an acute kidney injury, with creatinine increasing from baseline of 0.9 mg/dL to 1.4 mg/dL (0.67 to 1.24 mg/dL).

An i.v. insulin-dextrose infusion was commenced. A bolus of 20 mL of 50% dextrose was administered concurrently with 10% dextrose at a rate of 100 mL/h, with the plan being to start insulin infusion once blood glucose concentration exceeded 108 mg/dL (6.0 mmol/L) (Fig. 1).

Despite i.v. dextrose being infused (10–30 g/h) and stress-dose hydrocortisone being given, the patient only required 28 units of insulin by infusion in the first 24 h of treatment. Ketonemia rapidly resolved, and there was resolution of acidosis (Fig. 1). Neurological state improved to baseline at 24 h. Despite attempts to minimize fluid administration, the patient developed recurrent episodes of pulmonary edema requiring continuous positive airway pressure.

Bisoprolol, sacubitril-valsartan, and spironolactone were reintroduced sequentially. Empagliflozin was not restarted. Fasting PG was measured on three occasions in the 6 months following resolution of ketoacidosis. PG ranged from 73.8 to 84.6 mg/dL (4.1 to 4.7 mmol/L).

RESULTS

Here, we present the first two descriptions of severe ketoacidosis in patients without diabetes after treatment with SGLT2i for HFrEF (Table 1). Both patients presented with ketoacidosis triggered by reduced oral intake and, in the second case, a diarrheal illness resulting in reduced carbohydrate absorption. It is likely that reduced carbohydrate supply was compounded by continued SGLT2i-associated glucosuria and created a switch to

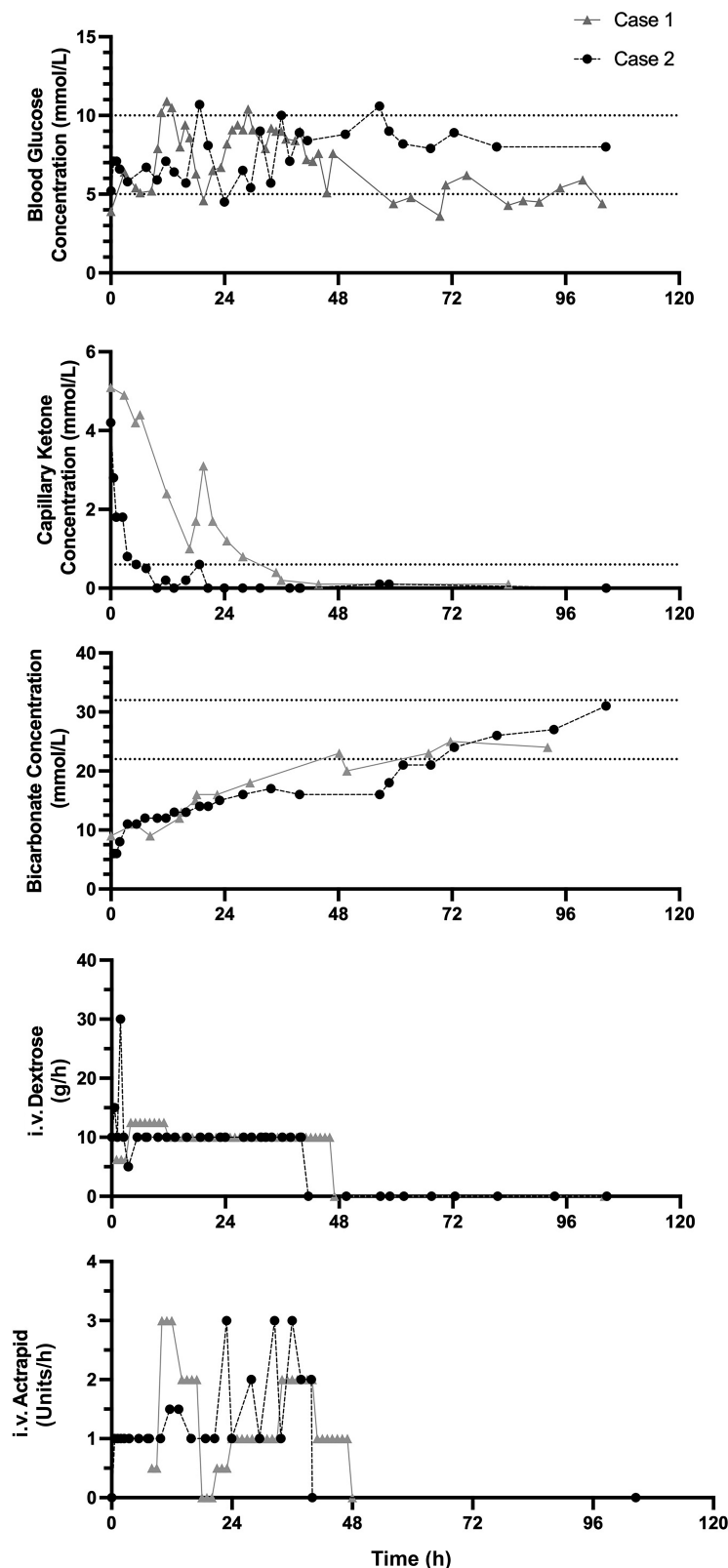


Figure 1—Response to insulin and dextrose infusion in patient without diabetes with SGLT2i-associated ketoacidosis. The graphs demonstrate the change in blood glucose, ketone, and bicarbonate concentrations over time with treatment of i.v. insulin and glucose infusion.

fatty acid metabolism and ketone production. In both instances, ketoacidosis resolved quickly with i.v. glucose

administration, encouragement of consumption of oral glucose-containing fluid, and minimal insulin administration. The

use of higher concentrations of i.v. dextrose was a deviation from the ketoacidosis protocol due to concern about triggering pulmonary edema and in an attempt to drive endogenous insulin secretion to suppress ketosis. To provide a point of comparison, in our institution the mean insulin dose in diabetic ketoacidosis (DKA) (i.v. and subcutaneous) is approximately 90 units in the first 24 h, and between 100 and 200 g of glucose is administered i.v., with a glucose-to-insulin ratio of 1.2–2.3 g/unit over the first 24 h. In the cases presented here, the glucose-to-insulin ratios were 11.1 and 9.1 g/unit for case 1 and case 2, respectively.

CONCLUSIONS

These two presentations confirm the possibility of SGLT2i-mediated euglycemic ketoacidosis in individuals without diabetes, even with adequate insulin secretory capacity. These cases support the proposed mechanism of reduced carbohydrate metabolism and lowering of blood glucose, resulting in elevation of glucagon and reduced insulin secretion, which leads to increased fat metabolism and formation of ketone bodies (14). C-peptide was measured after initiation of dextrose, and this likely masked the proposed reduction in insulin secretion associated with reduced carbohydrate supply. These cases suggest that rather than insulin deficiency or resistance, the driver of ketosis in SGLT2i use is carbohydrate loss, increased ketone body resorption, and a switch to fatty acid metabolism and ketosis to meet energy requirements in the context of acute illness (15).

The observation that individuals without diabetes can develop SGLT2i-associated ketoacidosis has significant implications for the management of these patients in high-risk ketogenic situations. Fasting periods for surgery, colonoscopy, or hospitalization have been identified as high-risk times for SGLT2i-associated ketoacidosis (6,7,16). In individuals with diabetes, guidelines suggest that SGLT2i should not be administered for 3 days prior to high-risk situations (e.g., surgery or colonoscopy); however, SGLT2i should be continued if an individual does not have diabetes (12). If our patients had not taken their SGLT2i at the beginning of their illness, the risk of presentation with DKA may have been reduced but not eliminated, as evidenced by prolonged glucosuria in case 1.

Table 1—Presentation biochemistry and treatment of SGLT2i-associated ketoacidosis

Parameter	Case 1	Case 2
Presentation plasma glucose, mg/dL, mmol/L	70.2, 3.9	77.4, 4.3
Presentation ketone, mmol/L (<0.6 mmol/L)	5.1	4.2
Presentation lactate, mmol/L (0.2–2.0 mmol/L)	1.2	0.9
Presentation anion gap, mmol/L (7–17 mmol/L)	25	29
Presentation bicarbonate, mmol/L (22–32 mmol/L)	9	6
Presentation pH	7.14	6.99
HbA _{1c} prior to commencement (%)	5.2	NA
Random PG prior to commencement, mmol/L	4.9	4.3
Time to resolution (h)	45	62
i.v. insulin administered in first 24 h (units)	22.5	28
C-peptide, mmol/L (366–1,466 pmol/L); paired PG, mg/dL, mmol/L	2,445; 138.6, 7.7	1,972; 77.4 4.3
Average dextrose rate over first 24 h, g/h	10.4	10.6

NA, not applicable. Normal values provided in parentheses.

These cases emphasize the need for ongoing research to document the frequency of SGLT2i-associated ketoacidosis in patients without diabetes. Even if the incidence of nondiabetic SGLT2i-associated ketoacidosis is uncommon, the widespread use of these agents for heart failure and renal dysfunction, as advocated by recent guidelines, suggest that this complication will be increasingly encountered (11,17). Physicians should have a high index of suspicion for ketoacidosis in individuals taking SGLT2i and consider offering patients who start an SGLT2i a sick-day management plan to reduce the risk of SGLT2i-associated ketoacidosis.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.M.U. drafted the manuscript and produced the figure. J.G. reviewed and assisted with manuscript production and data interpretation. S.N.S. reviewed the manuscript, assisted with manuscript production, and assisted with case identification. D.J. reviewed the

manuscript, assisted with manuscript production, and assisted with case identification. M.M.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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