Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium–Glucose Cotransporter 2 Inhibition

Anne L. Peters,[1] Elizabeth O. Buschur,[2] John B. Buse,[3] Pejman Cohan,[4] Jamie C. Diner,[3] and Irl B. Hirsch[5]

Diabetes Care 2015;38:1687–1693 | DOI: 10.2337/dc15-0843

OBJECTIVE

Sodium–glucose cotransporter 2 (SGLT-2) inhibitors are the most recently approved antihyperglycemic medications. We sought to describe their association with euglycemic diabetic ketoacidosis (euDKA) in hopes that it will enhance recognition of this potentially life-threatening complication.

RESEARCH DESIGN AND METHODS

Cases identified incidentally are described.

RESULTS

We identified 13 episodes of SGLT-2 inhibitor–associated euDKA or ketosis in nine individuals, seven with type 1 diabetes and two with type 2 diabetes, from various practices across the U.S. The absence of significant hyperglycemia in these patients delayed recognition of the emergent nature of the problem by patients and providers.

CONCLUSIONS

SGLT-2 inhibitors seem to be associated with euglycemic DKA and ketosis, perhaps as a consequence of their noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion. Patients with type 1 or type 2 diabetes who experience nausea, vomiting, or malaise or develop a metabolic acidosis in the setting of SGLT-2 inhibitor therapy should be promptly evaluated for the presence of urine and/or serum ketones. SGLT-2 inhibitors should only be used with great caution, extensive counseling, and close monitoring in the setting of type 1 diabetes.

Sodium–glucose cotransporter 2 (SGLT-2) inhibitors are the newest class of antihyperglycemic medications, first marketed in 2013 for the treatment of type 2 diabetes (1). Limited studies suggest that SGLT-2 inhibitors may be effective in addressing many of the unmet needs of people with type 1 diabetes, including improving average glycemia, while reducing glycemic variability and postprandial hyperglycemia, without increasing hypoglycemia, as well as promoting weight loss while reducing insulin doses (2–8). As a result, off-label use of SGLT-2 inhibitors in the setting of type 1 diabetes is increasing (8).

Diabetic ketoacidosis (DKA) is a well recognized complication of management of type 1 diabetes; nearly 5% of 6,796 adult participants with type 1 diabetes in the T1D Exchange program experienced one or more episodes of DKA within the past 12 months (9). DKA is traditionally defined by the triad of hyperglycemia (>250 mg/dL [>13.9 mmol/L]), anion-gap acidosis, and increased plasma ketones (10). Euglycemic DKA (euDKA), defined as DKA without marked hyperglycemia, is classically considered rare but this is perhaps a result of underrecognition and underreporting (10–12). euDKA is thought to be facilitated by factors such as partial treatment of

[1]*Keck School of Medicine of the University of Southern California, Los Angeles, CA*
[2]*The Ohio State University College of Medicine, Columbus, OH*
[3]*University of North Carolina School of Medicine, Chapel Hill, NC*
[4]*Specialized Endocrine Care Center, Beverly Hills, CA*
[5]*University of Washington School of Medicine, Seattle, WA*

Corresponding author: Anne L. Peters, momofmax@mac.com.

Received 21 April 2015 and accepted 21 May 2015.

See accompanying articles, pp. 1638 and 1680.

DKA, food restriction, alcohol intake, and inhibition of gluconeogenesis (10). Alcoholic ketoacidosis, a subtype of euglycemic ketoacidosis that occurs in individuals without diabetes, is thought to be underdiagnosed and is similar in presentation to euDKA although often with frankly low glucose values (12). In both DKA and alcoholic ketoacidosis, there is a decreased insulin secretion in the setting of increased counterregulatory hormone secretion (cortisol, glucagon, catecholamines, and growth hormone) (13).

Here we describe 13 cases of SGLT-2 inhibitor–associated euDKA or ketosis in nine individuals, seven with type 1 diabetes and two with type 2 diabetes, from various practices across the U.S. The absence of significant hyperglycemia in these individuals delayed recognition of the emergent nature of the problem by patients and providers.

RESEARCH DESIGN AND METHODS

One of us became aware of a case described and contacted many collaborators regarding the unusual finding, and cases were aggregated by the authors based on incidental experience without a systematic assessment of databases or clinical records. These efforts were reviewed and authorized by the University of Southern California Health Sciences and University of North Carolina at Chapel Hill Institutional Review Boards.

RESULTS

Table 1 presents nine patients with 13 episodes of euDKA or ketosis in the setting of treatment with SGLT-2 inhibitors. Among these patients, three had repeat episodes of ketosis on rechallenge. None of these patients had any prior episode of DKA other than at the diagnosis of diabetes (and no history of DKA in the patients with type 2 diabetes). No alcohol was ingested before the euDKA occurred except in the two patients where it is noted. In the female patients of childbearing age, pregnancy tests were negative. Narrative of the individual patients is provided below.

Case patient #1 was a 40-year-old woman with type 1 diabetes and a BMI of 26.5 kg/m^2 treated with a multiple daily insulin regimen (MDI) who was started on canagliflozin. Before initiating canagliflozin, her baseline A1C was 11.4% (101.1 mmol/mol). Two weeks after

Table 1—Clinical characteristics of euDKA cases

Case patient	1	2	3	4	5	6	7	8	9
Age (years)	40	58	27	28	31	55	26	39	64
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Female
T1/T2	T1	T2	T1	T1	T1	T1	T1	T1	T2
MDI/CSII	MDI	N/A	MDI	CSII	CSII	CSII	CSII	CSII	N/A
Duration (years)	17	2	25	6	15	18	13	26	6
BMI (kg/m^2)	26.5	26.5	24.3	25.9	33.2	22.0	22.0	26.1	32.8
Prior A1C [% (mmol/mol)]	11.4 (101.1)	9.8 (83.6)	7.8 (61.7)	8.0 (63.9)	7.0 (53.0)	7.2 (55.2)	6.6 (48.6)	7.0 (53.0)	7.8 (62.0)
Canagliflozin dose (mg)	300	300	300 100	300 100	300	300	150	300	300
Potential contributors	URI	Surgery 1 week prior	URI, alcohol	Alcohol	Exercise, alcohol	GI	None	URI	Surgery 12 h prior
Insulin dose reduction just prior to euDKA	Yes	N/A	Yes	No	Yes	Yes	Unknown	No	No	Yes	N/A
Presenting plasma glucose [mg/dL (mmol/L)]	220 (12.2)	150 (8.3)	150 (8.3)	96 (5.3)	224 (12.4)	158 (8.8)	~125 (~6.9)	203 (11.3)	190 (10.6)	150 (8.3)	233 (12.9)	169 (9.4)
pH	6.9	7.12	6.89						7.15			
P_{CO_2} (mmHg)	10								26			
Bicarbonate (mEq/L)	6	10	6		11	18		15	9		9	13 and then 5
Anion gap (mEq/L)	25	17	35		22	18		26	21		24	16 and then 19
Ketones*	Yes (serum and urine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (serum and urine)
Where treated	ICU	ICU	ICU	Outpt.	ICU	Inpt.	Outpt.	ICU	ICU	Outpt.	Outpt.	ICU	ICU

CSII, continuous subcutaneous insulin infusion; GI, gastrointestinal; Inpt., inpatient; N/A, not available; Outpt., outpatient. *Urine ketones were strongly positive in all cases.

initiating the drug, the patient reduced her basal insulin dose by ~50% due to improved glycemic control, and the dose was increased to 300 mg/day. Approximately 2 weeks later, she developed a febrile illness with decreased oral intake and presented to an emergency department (ED) with tachypnea and tachycardia. Because of her illness, she had been consuming fewer carbohydrates and using less insulin, although the change in dose was not recorded. When she arrived in the ED, her point-of-care blood glucose value was 220 mg/dL (12.2 mmol/L), serum sodium was 142 mmol/L, and measured serum osmolality was 313 mOsm/kg. Serum ketones were positive. Her arterial blood gas showed a pH of 6.9, P_{CO_2} of 10, and P_{O_2} of 145. She had a normal chest X-ray but was intubated for agitation and respiratory distress. The ED physicians felt that she had an anion-gap acidosis not caused by DKA because of her lack of significant blood glucose elevation. She was treated with intravenous saline, antibiotics, and bicarbonate and was transferred to the intensive care unit (ICU). Because of persistence of the anion-gap acidosis of unknown etiology, hemodialysis was initiated and she was started on an intravenous insulin infusion, which ultimately treated her euDKA.

Case patient #2 was a 58-year-old man with type 2 diabetes receiving canagliflozin without any insulin, who was admitted for an elective sigmoid colectomy. His baseline A1C was 9.8% (83.6 mmol/mol). He did well postoperatively and was discharged on his original dose of canagliflozin (300 mg/day). Five days after discharge, he was readmitted with severe abdominal pain, emesis, hyperventilation, and poor oral intake. Initial laboratory studies are reported in Table 1 and summarized as follows: sodium, 133 mmol/L; anion gap, 17 mEq/L; glucose, 150 mg/dL (8.3 mmol/L); bicarbonate, 10 mEq/L; and creatinine, 1.17 mg/dL (103.48 μmol/L). Laboratory studies 15 hours later on the day of readmission showed glucose, 164 mg/dL (9.11 mmol/L); serum osmolality, 309 mOsm/kg; creatinine, 1 mg/dL (88.4 μmol/L); anion gap, 25 mEq/L; and sodium, 141 mmol/L. During the next 24 h, glucose values ranged from 150 to 180 mg/dL (8.3–10 mmol/L). Because of his recent colectomy, he underwent an exploratory laparotomy that was unrevealing. Postoperatively, he could not be extubated, due to hyperventilation presumed secondary to metabolic acidosis. After other etiologies of anion-gap acidosis were excluded, he was treated for euDKA with intravenous insulin and fluids, with resolution of the acidosis. His anti-glutamic acid decarboxylase and anti-pancreatic islet cell antibodies were negative, and he had a normal C-peptide (4.1 ng/mL [1.4 nmol/L]).

Case patient #3 was a 27-year-old woman with type 1 diabetes on MDI and canagliflozin (300 mg/day) for ~1 month. On the canagliflozin, her daily insulin requirement had been reduced by ~10–15%. Her baseline A1C was 7.8% (61.7 mmol/mol). A week before admission, she had an upper respiratory tract infection (URI). For 2 of the 3 days before admission, she did not administer insulin glargine because her morning blood glucose level was ~100 mg/dL (5.6 mmol/L). The night before admission, she had two glasses of wine with dinner, which was a common practice for her on the weekend. The morning of admission, she awoke with a plasma glucose of 150 mg/dL (8.3 mmol/L), vomited repeatedly, and had large urine ketones. She went to the ED, with a blood glucose of 150 mg/dL (8.3 mmol/L) and was hospitalized in the ICU for euDKA. Her laboratory results revealed a serum sodium of 147 mmol/L, creatinine of 1.1 mg/dL (97.2 μmol/L), blood urea nitrogen (BUN) of 16 mg/dL (5.7 mmol/L), and a calculated serum osmolality of 313 mOsm/kg. Her anion gap was 35 mEq/L, and her bicarbonate was 6 mEq/L. She was treated with intravenous fluids, glucose, and insulin. Figure 1 displays her continuous glucose monitor (CGM) tracing for this day.

After discharge, her morning urine ketones were negative for 1 month, so she restarted canagliflozin at 100 mg/day. Three days afterward, she developed nausea and large urine ketones with a plasma glucose level of 96 mg/dL (5.3 mmol/L). She had consumed two glasses of wine the night before. She took ondansetron, drank carbohydrate-containing fluids, and administered rapid-acting insulin, and the ketonuria and nausea resolved.

Figure 1—One-day CGM reading of case patient #3 on the day of admission to the ICU in euDKA.

Case patient #4 was a 28-year-old woman with a history of type 1 diabetes treated with an insulin pump and canagliflozin (300 mg/day). Before initiating canagliflozin, her baseline A1C was 8.0% (63.9 mmol/mol). The night she developed euDKA, 1 month after starting the drug, she had been at a bar with friends and consumed two to three alcoholic beverages, something she did commonly. During the evening she began vomiting and had a reduction in consciousness. She was taken to the ED and then admitted for euDKA. Whether she reduced her insulin dose on the canagliflozin was unclear. At admission, her blood glucose level was 224 mg/dL (12.4 mmol/L), sodium was 136 mmol/L, CO_2 was 11 mmol/L, anion gap was 22 mEq/L, BUN was 20 mg/dL (7.14 mmol/L), creatinine was 0.67 mg/dL (59.2 μmol/L), and calculated serum osmolality was 293 mOsm/kg. Serum and urine ketones were positive. Her euDKA resolved with intravenous insulin and fluids.

She restarted canagliflozin a few days after discharge. Three weeks later, because she was walking for many hours, she administered less insulin. At dinner she consumed one beer and felt nauseated, developing a low blood glucose level, but after treatment continued to feel dizzy and vomited so she was taken to an ED. Initially, she did not appear to have euDKA. Her initial blood glucose level was 221 mg/dL (12.3 mmol/L), her CO_2 was 24 mmol/L, BUN was 19 mg/dL (6.78 mmol/L), and creatinine 0.8 mg/dL (70.72 μmol/L), although her anion gap was 17 mEq/L. She had strongly positive urine glucose and ketones. In the ED her pump was stopped, she was given intravenous saline, and the sliding scale insulin that was ordered was not given because her blood glucose values were 121–177 mg/dL (6.7–9.8 mmol/L). After several hours her blood glucose was 158 mg/dL (8.78 mmol/L) and her CO_2 fell to 18 mmol/L, with an anion gap of 18 mEq/L. She was then restarted on her insulin pump and given oral carbohydrates, with resolution of her euDKA.

Case patient #5 was a 31-year-old woman on insulin pump therapy treated with canagliflozin (300 mg/day) with a baseline A1C of 7.0% (53 mmol/mol). She became ill when she walked for 12 h through an amusement park and reduced her regular insulin dose. The next morning, day 1 of presumed euglycemic ketosis, she awoke with a severe headache and nausea not relieved with her migraine medications. On day 2, she was vomiting and had a blood glucose level of ~120 mg/dL (6.6 mmol/L). On day 3, she went to an urgent care center where she was treated with promethazine and ondansetron without relief. On day 5, she saw a neurologist who started her on oral steroids for the refractory headache. Before she started the steroids, she contacted her endocrinologist who instructed her to test for urine ketones, which were strongly positive. The patient self-managed the euglycemic ketosis with frequent oral glucose–containing fluids, insulin, and antiemetics; as her ketones resolved, so did her headache, nausea, and vomiting.

Case patient #6 was a 55-year-old woman with an 18-year history of type 1 diabetes treated with an insulin pump and canagliflozin. Her baseline A1C was 7.2% (55.2 mmol/mol). She developed nausea and vomiting several hours after eating in a restaurant and assumed her symptoms were due to food poisoning. Blood glucose at home remained ~110 mg/dL (6.1 mmol/L). The vomiting did not resolve, and after several hours, she was taken to the ED where she was found to have an anion-gap acidosis with a blood glucose of 203 mg/dL (11.3 mmol/L) and large ketonuria. Her anion gap was 26 mEq/L and her bicarbonate was 15 mEq/L. She was treated for euDKA and recovered uneventfully.

Case patient #7 was a 26-year-old woman with a baseline A1C of 6.6% (48.6 mmol/mol) who had been treated for her type 1 diabetes with insulin pump therapy, liraglutide, and canagliflozin. She had been taking the canagliflozin for a month and a half and had reduced her basal and bolus insulin by ~25% due to improved control. During the night preceding the event, the patient had taken additional insulin boluses for minimal hyperglycemia. In the morning, she awoke with nausea and vomiting and presented to the ED where euDKA was recognized with a venous blood gas. She had an anion gap of 21 mEq/L and a bicarbonate value of 9 mEq/L. Her CGM tracing is shown in Fig. 2. She was admitted to the medical ICU and responded to intravenous fluids and insulin. After discharge, she discontinued the liraglutide and continued the

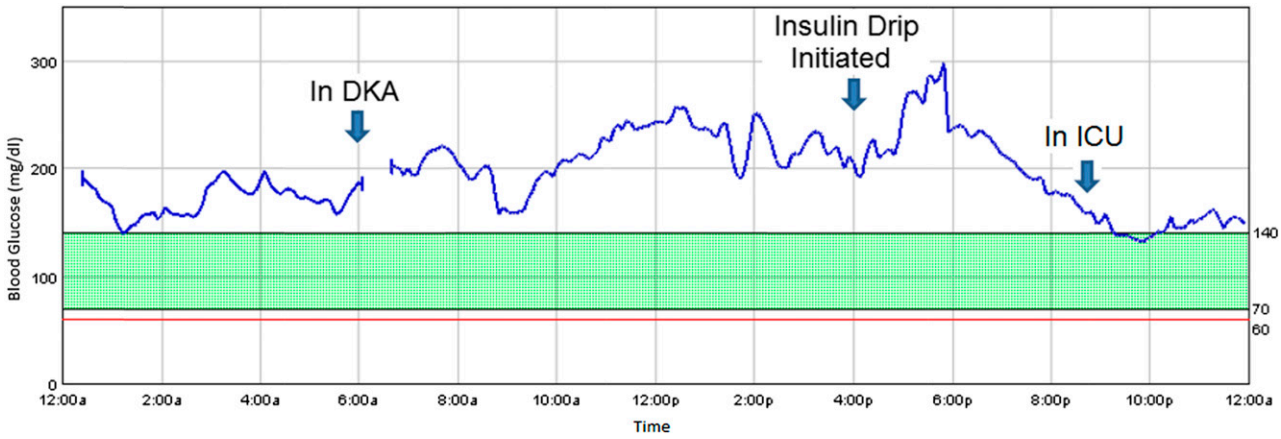

Figure 2—One-day CGM reading of case patient #7 the day of admission to the ICU in euDKA.

canagliflozin but had large ketonuria, despite relative euglycemia, which she treated with additional doses of insulin and oral carbohydrates. During the last of the events, the patient had not taken her dose of canagliflozin for more than 48 h, yet still had strongly positive urine ketones in the morning. The patient reported consuming no alcohol near the time of any of these events. Subsequently, the canagliflozin was discontinued without recurrence of ketonuria.

Case patient #8 was a 39-year-old woman with 26-year history of type 1 diabetes managed on an insulin pump and canagliflozin. Before initiating canagliflozin, her baseline A1C was 7.0% (53.0 mmol/mol). She had a 2-week history of a URI with possible pneumonia. She was slowly recovering, although the day of admission she felt somewhat nauseated and reduced her oral intake and bolus insulin. Her husband returned home from a business trip and found her weak and nauseated, with Kussmaul respirations. He took her to an ED where she was diagnosed with euDKA with an anion gap of 24 mEq/L and a bicarbonate of 9 mEq/L. She was admitted to the medical ICU and treated uneventfully. She was discharged after 36 h in the hospital.

Case patient #9 was a 64-year-old overweight woman (BMI 32.8 kg/m^2) with type 2 diabetes who was admitted for elective bilateral cervical foraminotomy. She was anti-GAD negative and C-peptide positive. Before starting canagliflozin, she had been taking glyburide, sitagliptin, and detemir (20 units twice daily). Her A1C was 8.4% (68 mmol/mol) when she was started on canagliflozin, which was uptitrated to 300 mg/day. During the next 6 months, she lost weight (BMI 29.1 kg/m^2), was able to stop her insulin, and reduced her A1C to 7.8% (62 mmol/mol). Her canagliflozin was held the morning of surgery. She developed nausea ~10 h after the procedure. By the next morning, her CO_2 was 13 mmol/L, with a blood glucose of 169 mg/dL (9.39 mmol/L) and an anion gap of 16 mEq/L. The patient's nausea and vomiting was treated with antiemetics. The next morning her blood glucose was 179 mg/dL (9.94 mmol/L), CO_2 was 5 mmol/L, anion gap was 19 mEq/L, and measured serum osmolality was 318 mOsm/kg. By evening, her endocrinologist was notified, who measured her serum acetone level (positive at a 1:32 dilution) and started an intravenous insulin drip along with intravenous dextrose. During the next few days in the ICU, her CO_2 increased progressively to normal, and her blood glucose levels were in the range of 116 to 190 mg/dL (6.44–10.56 mmol/L). Her complete metabolic recovery occurred ~6 days after her last dose of canagliflozin.

CONCLUSIONS

This is the first case series of euDKA associated with use of SGLT-2 inhibitors. These agents, by inhibiting glucose reabsorption, promote glycosuria, lower plasma glucose, and induce modest weight loss (1). SGLT-2 inhibitors have been approved for use in people with type 2 diabetes, and clinical trials are on-going in individuals with type 1 diabetes. Two prior cases of euDKA with SGLT-2 inhibitors have been reported. One was in a woman who had type 2 diabetes as well as Prader-Willi syndrome treated with a low-carbohydrate diet who developed euDKA while on ipragliflozin (14). The other was a man with type 1 diabetes who was not entirely forthcoming about the medications he had been taking. Although it seems he was taking canagliflozin, whether he was still administering insulin was not clear (15).

The most important feature in all of these initial cases is that the patients did not recognize they had ketoacidosis, which is typically associated with severe hyperglycemia. As a result, instead of increasing insulin doses, insulin was unchanged or decreased. When patients presented for acute medical care, their providers often failed to recognize the DKA, leading to unnecessary testing and treatment. All of the patients reported here were treated with canagliflozin, likely because it was first to market and has the greatest exposure in the population. Other SGLT-2 inhibitors are similar in action, and we speculate that they are likely to pose similar risk for euDKA. The overall risk for developing euDKA on SGLT-2 inhibitors is unknown; ongoing trials should further define the risk, particularly in type 1 diabetes and postoperatively in individuals with type 2 diabetes. All of the patients presented are quite similar biochemically and all responded readily to intravenous fluids and insulin once the syndrome was recognized. Although alcohol intake was included as a potential contributor in some of the patients, most of the patients denied recent or excessive alcohol use. Most of the patients were women, but there were no consistent patterns in age or BMI. In the patients with type 1 diabetes, concomitant mild infection, increased activity, and/or reduced food intake coupled with acute insulin dose reduction or omission were potential contributors in many patients, whereas in others, no contributing factors were identified. Many of the patients reported nausea; however, it seems more likely than not that nausea was a consequence instead of a contributor to the euDKA or ketosis in most patients.

The mechanism of euDKA is not fully elucidated. The first description was in a series of 37 patients (mean age 18.6 years; range 10–28) who presented with DKA and a blood glucose level of less than 300 mg/dL (16.7 mmol/L) (11). Vomiting was seen in 32% and was the most common presenting feature. Interestingly, although the authors were not able to explain the phenomenon, a letter to the editor opined that the cause of the euDKA was due to a lower renal threshold for glucose and a loss of large amounts of glucose in the urine in the presence of an increased rate of gluconeogenesis and free fatty acid release (16), foreshadowing the findings in this case series. A recent publication from Japan similarly suggested this potential mechanism for euDKA with SGLT-2 inhibition, without reporting the details in the one patient identified (17).

Increased renal clearance of glucose mediated by the SGLT-2 inhibitor led to deceivingly low blood glucose levels in the setting of illness, and the reduced insulin doses at a time of heightened insulin resistance may have tipped the balance toward ketosis resulting in euDKA. In our series, illness and a reduction in food intake and/or insulin doses preceded the development of DKA in some but not all patients. Normally, fasting glucose reflects hepatic glucose production, inhibited at relatively low portal insulin concentrations. Suppression of ketogenesis requires somewhat higher insulin levels (18). Arguably, in the setting of SGLT-2 inhibition, fasting glucose can be maintained at reasonable levels despite very low portal

insulin because of urinary glucose loses. This may predispose to ketosis and, most importantly, may uncouple ketosis from the finding of severe hyperglycemia. Furthermore, SGLT-2 inhibitors are associated with an increase in plasma glucagon levels through uncertain mechanisms (19,20). Hyperglucagonemia increases the propensity toward ketone production (21). Through their mechanism of action, SGLT-2 inhibitors also predispose to a negative fluid and sodium balance and may thereby compound the already hypovolemic state of DKA, particularly in the setting of nausea and poor oral intake. Hypovolemia drives elevations in glucagon, cortisol, and epinephrine, which further increase insulin resistance, lipolysis, and ketogenesis.

In conclusion, euDKA appears to be a worrisome adverse event associated with SGLT-2 inhibitor use in patients with type 1 and type 2 diabetes. During the preparation and review of this article, a similar number of additional cases of euDKA in patients with type 1 and type 2 diabetes treated with SGLT-2 inhibitors were reported to us by reviewers and collaborators; thus, we suspect that this is not a rare occurrence, particularly in type 1 diabetes. Further, during review the U.S. Food and Drug Administration posted a warning based on 20 cases of acidosis with ketosis in the setting of SGLT-2 inhibitor therapy, largely in patients with in type 2 diabetes (22). While the frequency and mechanism of this complication require more study, clinicians and patients need to appreciate the potential risk when prescribing these agents.

At this time, SGLT-2 inhibitors are not approved by regulatory authorities in the setting of type 1 diabetes. If a clinician and patient with type 1 diabetes decide that the benefits of off-label use of SGLT-2 inhibitors outweigh the risks, the patient should be carefully and extensively counseled regarding the observations reported and, at a minimum, instructed to check urine or blood ketones if he or she feels unwell, even if plasma glucose is normal. Arguably, even greater vigilance for symptoms and ketonuria should be exercised in the setting of more than minimal alcohol consumption or if insulin doses are reduced for any reason, including for prolonged exercise or reduced carbohydrate intake. Early detection of ketosis could likely prevent patients from deteriorating; however, patients are generally asymptomatic until they have developed euDKA. The only way to ensure timely recognition would be to use daily urine or blood ketone testing. If moderate or large urine ketones are present, patients should be instructed by their providers to automatically withhold SGLT-2 inhibitor use at least temporarily, to contact their provider, to maintain vigorous hydration, and to consume carbohydrates to allow at least full-dose insulin therapy until ketones resolve. If for any reason the patient is not able to take liquids and carbohydrates liberally or self-monitor carefully, it would be prudent for the patient to seek medical attention promptly in a setting where intravenous fluids can be administered.

Although the U.S. Food and Drug Administration guidance (22) to the general public suggests "do not stop or change your diabetes medicines without first talking to your prescriber," we believe this refers to patients with type 2 diabetes who are currently taking SGLT-2 inhibitors on-label and doing well on the therapy without DKA. Individuals with type 2 diabetes do not need to monitor their urine ketones, but it is important that providers recognize that euDKA can occur in any individual with type 1 or type 2 diabetes taking an SGLT-2 inhibitor. Our advice to providers treating patients with type 1 diabetes off-label would be to withhold SGLT-2 inhibitor therapy if patients experience minimally symptomatic moderate to large ketonuria or ketonemia. Obviously, this is an issue that needs to be worked out between patients and providers individually. More importantly, if a patient develops DKA in the setting of SGLT-2 inhibitor therapy, the SGLT-2 inhibitor should be not be restarted immediately because two of the patients reported here who continued SGLT-2 inhibitor therapy had recurrences of DKA or symptomatic ketosis.

Both of the cases of euDKA in patients with type 2 diabetes occurred in the postoperative period. The potential for postoperative euDKA in the setting of SGLT-2 inhibitor therapy deserves special attention because the exact duration of the metabolic effects of the SGLT-2 inhibitors are not known. Although they have a half-life of ~12 h, the pharmacodynamic effects could last longer and simply stopping the drug 24–48 h before surgery may have little effect. We hope that future research will provide guidance for specific recommendations in the perioperative setting. Given the occurrence of euDKA in two individuals with type 2 diabetes, it would be prudent to be aware of this complication for patients with type 2 diabetes, particularly those with a history of DKA (23) or who are in the postoperative period.

Finally, awareness that DKA can occur in the setting of relative euglycemia is critical to recognize this life-threatening complication of diabetes. All patients with type 1 or type 2 diabetes who experience nausea, vomiting, shortness of breath, or malaise in the setting of SGLT-2 inhibitor therapy should be promptly evaluated for urine and/or plasma ketones at home or in a medical setting, even if glucose levels are nearly normal.

Acknowledgments. The authors thank referring and collaborating clinicians for their assistance and patients for allowing to share their stories. The authors also thank Dr. Silvio Inzucchi (Yale University) for his insights into the etiology of this phenomenon.

Funding. J.B.B. was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number 1UL1-TR-001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Duality of Interest. A.L.P. has been an investigator, speaker, and/or consultant for Abbott Diabetes Care, Amgen, AstraZeneca, BD, Biodel, BMS, Boehringer Ingelheim, Janssen, Lexicon, Eli Lilly, Medtronic, Merck, Novo Nordisk, OptumRx, Sanofi, Takeda, and Thermalin. J.B.B. is an investigator and/or consultant without any direct financial benefit under contracts between his employer and the following companies: Andromeda, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dance Pharmaceuticals, Elcelyx, Eli Lilly, GI Dynamics, GlaxoSmithKline, Halozyme, Hoffmann-La Roche, Intarcia Therapeutics, Johnson & Johnson, Lexicon, LipoScience, Medtronic, Merck, Metabolic Solutions Development Company, Metabolon, Metavention, Novartis, Novo Nordisk, Orexigen, Osiris, Pfizer, Rhythm, Sanofi, Takeda, Tolerex, Transtech Pharma, Veritas, and Verva. J.B.B. is a consultant for and has received stock options from PhaseBio. I.B.H. receives research grants from Sanofi, Novo Nordisk, and Halozyme and is a consultant for Abbott Diabetes Care, Roche, and Valeritas. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.L.P., E.O.B., J.B.B., P.C., J.C.D., and I.B.H. participated in identifying patients and in drafting and editing the

manuscript. A.L.P. 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.

References

1. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011; 378:182–197
2. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015;38:412–419
3. Lamos EM, Younk LM, Davis SN. Empagliflozin, a sodium glucose co-transporter 2 inhibitor, in the treatment of type 1 diabetes. Expert Opin Investig Drugs 2014;23:875–882
4. Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care 2014;37:1480–1483
5. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129: 587–597
6. Rosenstock J, Cefalu WT, Lapuerta P, et al. Greater dose-ranging effects on A1C levels than on glucosuria with LX4211, a dual inhibitor of SGLT1 and SGLT2, in patients with type 2 diabetes on metformin monotherapy. Diabetes Care 2015;38:431–438
7. Powell DR, DaCosta CM, Smith M, et al. Effect of LX4211 on glucose homeostasis and body composition in preclinical models. J Pharmacol Exp Ther 2014;350:232–242
8. Bell DS. Case reports that illustrate the efficacy of SGLT2 inhibitors in the type 1 diabetic patient. Case Rep Endocrinol 2015;2015:676191
9. Weinstock RS, Xing D, Maahs DM, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and DKA in adults with T1D: results from the T1D exchange clinic registry. J Clin Endocrinol Metab 2013;98:3411–3419
10. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–1343
11. Munro JF, Campbell IW, McCuish AC, Duncan LJP. Euglycaemic diabetic ketoacidosis. BMJ 1973;2:578–580
12. McGuire LC, Cruickshank AM, Munro PT. Alcoholic ketoacidosis. Emerg Med J 2006;23: 417–420
13. Umpierrez GE, DiGirolamo M, Tuvlin JA, Isaacs SD, Bhoola SM, Kokko JP. Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. J Crit Care 2000;15:52–59
14. Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Invest. 20 February 2015 [Epub ahead of print]. DOI: 10.1111/jdi.12330
15. St Hilaire R, Costello H. Prescriber beware: report of adverse effect of sodium-glucose cotransporter 2 inhibitor use in a patient with contraindication. Am J Emerg Med 2015:33:604.e3–e4
16. Ireland JT, Thomson WS. Euglycemic diabetic ketoacidosis. BMJ 1973;3:107
17. Yabe D, Nishikino R, Kaneko M, Iwasaki M, Seino Y. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. Expert Opin Drug Saf 2015;14:795–800
18. Groop LC, Bonadonna RC, DelPrato S, et al. Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J Clin Invest 1989;84:205–213
19. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508
20. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–514
21. Keller U, Schnell H, Sonnenberg GE, Gerber PPG, Stauffacher W. Role of glucagon in enhancing ketone body production in ketotic diabetic man. Diabetes 1983;32:387–391
22. FDA Drug Safety Communication. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available from http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed 15 May 2015
23. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006;144:350–357