FEATURE ARTICLE

Comparison of Protocols to Reduce Diabetic Ketoacidosis in Patients With Type 1 Diabetes Prescribed a Sodium–Glucose Cotransporter 2 Inhibitor

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OBJECTIVE | Sodium–glucose cotransporter 2 (SGLT2) inhibitors are approved for type 1 diabetes in Europe and Japan, with off-label use in type 1 diabetes in the United States. Although there were no consistent approaches to risk mitigation in clinical trials of these agents, protocols have been developed to try to reduce the risk of diabetic ketoacidosis (DKA). However, a validated risk mitigation strategy does not exist. We reviewed available DKA risk mitigation protocols to better understand the various strategies currently in use.

METHODS | We conducted a search of the published medical literature and other medical information sources, including conference presentations, for protocols. We then categorized the information provided into guidance on patient selection, initiation of SGLT2 inhibitors, ketone monitoring, necessary patient action in the event of ketosis or DKA, and inpatient treatment of ketosis or DKA.

RESULTS | Patient selection is generally similar among the protocols, although some require a minimum BMI and insulin dose. All protocols advocate routine measurement of ketones, although some insist on blood ketone tests. Although action steps for ketosis varies, all protocols advocate rapid patient intervention. The importance of evaluating ketones and acid-base balance even in the absence of hyperglycemia is emphasized by all protocols, as is the need to continue administering insulin until ketosis has resolved.

CONCLUSION | DKA risk mitigation must be pursued systematically in individuals with type 1 diabetes, although the best strategy remains to be determined. Given the ongoing need for adjunctive therapies in type 1 diabetes and current use of SGLT2 inhibitors for this purpose, additional education and research are crucial, especially in the hospital environment, where DKA may not be diagnosed promptly and treated appropriately.

Despite nearly a century having passed since the discovery of insulin, the majority of people with type 1 diabetes still are not at their target A1C (1,2). Thus, there has been increasing interest in adjunctive therapies beyond insulin that can benefit both immediate glycemic management and downstream long-term complications (3). However, pramlintide, an amylin analog, is the only noninsulin treatment currently approved for type 1 diabetes by the U.S. Food and Drug Administration (FDA) (4).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which block reabsorption of urinary glucose and induce glucosuria, have been identified as a class of drugs with major potential for use in type 1 diabetes management (5). SGLT2 inhibitors may be a desirable therapy for people with type 1 diabetes because they have been shown to reduce glycemic variability and A1C and yield weight loss, while not increasing rates of hypoglycemia (6–11). Furthermore, although it is unknown whether documented long-term cardiovascular and renal benefits of SGLT2 inhibition in type 2 diabetes will translate to type 1 diabetes, even people without diabetes are now being prescribed these agents for heart failure and chronic kidney disease, so it seems likely that these benefits will extend to all.

Unfortunately, SGLT2 inhibitors increase the risk for diabetic ketoacidosis (DKA) (12,13). This increase in risk is small in people with type 2 diabetes (12) but larger in those with type 1 diabetes (14). In phase 2 and 3 clinical trials in individuals with type 1 diabetes, only the 2.5-mg dose of

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empagliflozin in the EASE-3 (Empagliflozin as Adjunctive to Insulin Therapy 3) trial showed rates of DKA similar to placebo with less reduction in A1C (7).

Regardless of such findings, SGLT2 inhibitors are approved for use in individuals with type 1 diabetes in Europe (15,16) and Japan (17) and are being used off-label in these patients in the United States. Hence, a number of protocols have been developed to try to reduce the risk of DKA for individuals with type 1 diabetes who choose to use SGLT2 inhibitors. In the clinical trials performed to date, there was not a consistent approach to risk mitigation, and all of the strategies used seemed to be lacking in some manner. Therefore, there is no validated risk mitigation strategy to follow at present. In this article, we review the current landscape of DKA risk mitigation with SGLT2 inhibitors to provide a comprehensive understanding of the various protocols currently in use.

Research Design and Methods

We performed a search of published medical literature (PubMed) and other sources of medical information, including presentations at recent conferences, for protocols. Search terms of the published medical literature included "type 1 diabetes," "(SGLT-2 or SGLT) inhibitors," and "ketoacidosis." We identified three published protocols: Danne et al.'s International Consensus protocol (18), Goldenberg et al.'s STOP DKA protocol (19), and Garg et al.'s STICH (STop SGLT inhibitor treatment, Insulin administration, Carbohydrate consumption, Hydration with water or sugar-free electrolyte drink) protocol (20). In addition, the European Medicines Agency (EMA) product information for dapagliflozin and sotagliflozin (15,16) and the U.K.'s National Institute for Health and Care Excellence (NICE) guidance on dapagliflozin and sotagliflozin (21,22) contain relevant information for health care providers (HCPs) and were therefore included. Lastly, we included an unpublished clinic protocol for off-label use of SGLT2 inhibitors developed by one of the coauthors (A.L.P.), which was presented at several recent conferences and posted in part on the Medscape website (14).

To try to organize the information provided in these protocols, we categorized the details into guidance on *1*) patient selection, *2*) initiation of SGLT2 inhibitors, *3*) ketone monitoring, *4*) self-management of ketosis/DKA, and *5*) hospital treatment of DKA.

Results

Patient Selection

All protocols agree that choosing which patients with type 1 diabetes are capable of adhering to a protocol and following DKA prevention instructions is key to success. Certain qualifying characteristics exist (Table 1). Patients should not be on a low-carbohydrate or ketogenic diet and should avoid excessive alcohol consumption or illicit drug use. Any situation that can lead to dehydration or escalating insulin doses may necessitate holding the SGLT2 inhibitor and testing ketone levels. Such situations include intensive exercise and illness. Interestingly, NICE requires a minimum insulin dosage of 0.5 units/kg body weight/day (21–23).

The EMA and NICE recommend only initiating SGLT2 inhibitors in patients with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2. In addition, the EMA specifies that patients should be <70 years of age. The EMA and NICE suggest a BMI cut point of ≥27 kg/m^2 to reduce the risk of DKA. This recommendation stems from a post hoc analysis from the DEPICT (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) research trials (DEPICT 1 and DEPICT 2), which showed that only 1.8% of patients on dapagliflozin and 1.0% of patients on placebo with a BMI >27 kg/m^2 experienced DKA compared with 4.0% of patients on dapagliflozin and 1.1% of patients on placebo with a BMI <27 kg/m^2 (24). Post hoc analysis of data for sotagliflozin was less convincing (25). The STICH and the International Consensus protocols do not mention this metric, whereas the STOP DKA protocol notes that "overweight or obese patients" are most suitable. In general, the unpublished clinic protocol has one of the most rigorous lists of requirements, which further mandates baseline ketones <0.6 mmol/L, a point also shared by the International Consensus and the EMA, and a baseline A1C <9.0%.

Only patients who are willing to measure ketones and can comprehend what the results mean should be started on an SGLT2 inhibitor. Although not highlighted in many of the protocols, monitoring baseline ketone levels is an important step in preparing for drug initiation. The unpublished clinic protocol recommends measuring daily fasting serum or urine ketones for 2 weeks before initiation and for 2 weeks after dose stabilization, using the data for clinical guidance. Patients with elevated baseline ketones should not be started on an SGLT2 inhibitor. The EMA guides patients to "obtain several baseline ketones" over 1–2 weeks before the SGLT2 inhibitor is started.

As shown in Table 1, a number of protocols only recommend prescription of SGLT2 inhibitors by HCPs who are adept in using the drug class or even those who have "24/7" availability to patients. Without broader physician education, which would likely be spurred by additional regulatory approvals (including approval in the United States), these requirements will limit the number of patients who are able to benefit from this therapy.

TABLE 1 Considerations for Patient Selection

	STICH (20)	International Consensus (18)	STOP DKA (19)	Anne L. Peters' Protocol (14)	EMA Guidance (11,12)	NICE Guidance (21–23)
Baseline A1C, %	NA	NA	NA	<9.0	NA	NA
Baseline ketones, mmol/L	NA	<0.6 or negative urine	NA	<0.6	<0.6 or negative urine	NA
BMI, kg/m^2	NA	NA	NA	NA	≥27	≥27
Insulin dose, units/kg	NA	NA	NA	NA	NA	>0.5
Lifestyle	• Caution with extreme athletic activities • Avoid excessive alcohol and very-low-carbohydrate or ketogenic diets	• Increased risk with insulin pump • Increased risk if skipped meals or excessive alcohol • Not for patients using low-carbohydrate or ketogenic diets	• Those with overweight or obesity are most suitable • Avoid very-low-carbohydrate or ketogenic diets • Avoid excessive alcohol • Caution with extreme exercise	• Monitoring blood glucose at least four times daily and/or on CGM • At least 100 g carbohydrates daily (not low-carbohydrate or ketogenic diet) • No alcoholism or drug abuse	• Correct volume depletion • eGFR >60 mL/min/1.73 m^2 • Only <75 years • No caloric or carb restriction, ketogenic diets, excess alcohol, or illicit drugs	• eGFR >60 mL/min/1.73 m^2 to initiate treatment
Necessary clinician access	Patients should call clinicians every 2–4 hours during possible DKA (while checking ketones)	• Only clinicians well trained in SGLT2i use in T1D • Immediate access to a clinician if ketones rise	Only prescribers who have expertise with T1D should prescribe	• 24/7 access to a knowledgeable health care provider • Patients should provide weekly blood glucose and ketone testing results and insulin doses to clinician	• Initiated and supervised by specialist in T1D • Immediate access to a clinician if ketones rise	Treatment started and supervised by a consultant physician specializing in endocrinology and diabetes
Necessary education/ resources	• Carry wallet card with information on DKA with SGLT2i • How and why SGLT2i increases DKA risk • Strategies to monitor/respond to ketosis	• Instruction in DKA risk factors, ketone monitoring, and treatment • Provided with educational materials (e.g., wallet cards and refrigerator magnets)	• Patients taught precipitating causes of ketosis and actions that should be taken during an acute illness with symptoms suggestive of ketosis/DKA • Ongoing education of both patients and providers	• Have patient acknowledge understanding of off-label use of medication and document in chart • Education on lifestyle recommendation and what to avoid • Pump patients should be counseled to always carry a pen/ syringe so insulin can be given in case of pump occlusion/ failure	Patients should be informed, in a dedicated education session, on the risk of DKA; how to recognize DKA risk factors, signs, or symptoms; how and when to monitor ketone levels; and what actions to take if ketones rise	Structured education program that is evidence based, quality assured, and delivered by trained educators that includes information about DKA; how to recognize risk factors; how and when to monitor blood ketone levels; and what actions to take for elevated blood ketones

All protocols include diligent adherence to regimen, no recent DKA or hyperglycemia, and no recurrent hypoglycemia or hyperglycemia and stipulate that this therapy is not for pregnant women or children <18 years of age. NA, not applicable; SGLT2i, SGLT2 inhibitor; T1D, type 1 diabetes.

Initiation of SGLT2 Inhibitors

Table 2 describes the different recommended approaches to initiation of treatment. All protocols suggest starting at a low dose of the SGLT2 inhibitor agent. The International Consensus also adds that some HCPs "even suggest splitting doses," although further details are not provided. In the unpublished clinic protocol, patients are started on one-fourth to one-half of a tablet of the lowest dose, with a gradual increase in dosage every 2 weeks based on ketone

TABLE 2 Considerations for Initiation of SGLT2 Inhibitor Therapy

	STICH (20)	International Consensus (18)	STOP DKA (19)	Anne L. Peters' Protocol (14)	EMA Guidance (11,12)	NICE Guidance (21–23)
Dosing	NA	• Initiate at lowest dose possible • Some HCPs even suggest splitting doses	Prescribe lower doses of SGLT2i	• Start SGLT2i in the morning, after ketone testing; do not take if BHB ≥6 mmol/L or urine has more than trace ketones • Start with one-fourth to one-half tablet of the lowest dose • Increase dose slowly every 2 weeks based on blood ketone levels	• Dapagliflozin 5 mg/day • Sotagliflozin 200 mg/day before first meal of day; may be increased after 3 months to two tablets (400 mg/day)	Dapagliflozin: 5 mg/day
Maximum dosage	NA	NA	NA	• Canagliflozin: 100 mg/day • Empagliflozin: 10 mg/day • Dapagliflozin: 5 mg/day • Ertugliflozin: 5 mg/day	• Dapagliflozin: 5 mg/day • Sotagliflozin: 400 mg/day	NA
Ketone monitoring before SGLT2i initiation	NA	NA	NA	• Measure daily fasting ketones for 2 weeks; report values to clinician weekly • Continue monitoring until stable on maximum dose for 2 weeks; once on stable dose of SGLT2i, monitor as needed routinely	Obtain several baseline ketones over 1–2 weeks before SGLT2i initiation	NA
Timing of insulin adjustment	During initiation and maintenance	At least every 24–48 hours initially	• During initial phase of SGLT2i use • Reassess once patient is stabilized on SGLT2i	Do not adjust insulin in advance or initially	• Adjust mealtime insulin with first dose • No reduction in basal insulin when initiating SGLT2i	NA
Adjustments in insulin dosage	• Clinicians should carefully monitor insulin dose reductions	• If switching insulin (injection to pump; manual to automatic delivery), hold SGLT2i until insulin doses are adjusted and blood glucose and ketones are normal • Clinicians need to individualize dose reductions • If glycemia is relatively well controlled (A1C <7.5%), 10–20% reduction in insulin doses • If glycemia is less well controlled (A1C ≥7.5%), slight or no reductions in prandial and basal insulin	• Insulin doses cautiously adjusted • Basal insulin doses modified based on blood glucose values • Try to avoid insulin dose reductions of >20% • Never stop insulin	• Clinicians should discuss that less premeal insulin may be required subsequently • Adjust dose using correction factor and insulin-to-carbohydrate ratio • Adjust insulin based on CGM when possible	• 20% reduction in first mealtime bolus insulin may be considered with first dose of dapagliflozin/sotagliflozin • No initial reduction in basal insulin is recommended • Subsequently, basal insulin should be adjusted based on blood glucose results	• During treatment with dapagliflozin, insulin therapy should be continuously optimized to prevent ketosis and DKA • Insulin dose should only be reduced to avoid hypoglycemia

NA, not applicable; SGLT2i, SGLT2 inhibitor.

levels. The maximum doses used in that protocol are canagliflozin 100 mg/day, empagliflozin 10 mg/day, dapagliflozin 5 mg/day, and ertugliflozin 5 mg/day.

Protocol recommendations in terms of insulin dose adjustments vary significantly, and although it can be expected that adjustments will change on a patient-by-patient basis, more data are needed to set even foundational basic rules for treatment. Table 2 lists the recommended insulin dose adjustments from each protocol. Only the unpublished protocol does not recommend anticipatory insulin dose adjustments, but rather suggests waiting to see the patient's response and then adjusting accordingly. In this protocol, a very low initial dose of SGLT2 inhibitor is used, and patients are all on either multiple daily insulin injections or insulin pump therapy and adjusting doses using a correction factor and insulin-to-carbohydrate ratio. Most patients using this protocol are on continuous glucose monitoring (CGM) and using Tidepool, the data management application (26), for insulin dose adjustments. Additionally, in some cases to avoid ketosis, carbohydrate intake is increased rather than decreasing the insulin dose.

Ketone Monitoring

Given the risk of DKA, the importance of having familiarity with ketone monitoring cannot be overstated (Table 3). Although it is widely accepted that monitoring of blood ketone (β-hydroxybutyrate [BHB]) levels is more accurate than urine ketone monitoring of acetoacetate levels, devices and strips for testing blood ketone levels are generally more expensive and a less accessible option, with variable insurance coverage. There is a lack of consensus regarding the frequency with which any type of ketone monitoring should be performed. Ketones can either be monitored anticipatorily when they might become positive (such as with increased exercise, dehydration, infusion set failure, or increased alcohol ingestion) or only when a person has symptoms of ketosis or ketoacidosis.

Self-Management of Ketosis/DKA

All protocols stress the need for patients to be educated regarding how to self-treat elevated ketone levels. The blood or urine ketone ranges for each stage of ketonemia/DKA vary slightly among the protocols (Table 4), with the biggest distinction being that STOP DKA defines mild ketonemia as <1.0 mmol/L versus 0.6 mmol/L in most of the other protocols. SGLT2 inhibitors should be held as soon as any symptoms of physical illness (e.g., lethargy, loss of appetite, nausea, or abdominal pain) or elevated ketone levels are detected and reinstated only when ketone levels return to normal. Generally, patients should consume carbohydrates and give insulin in an attempt to lower ketone levels. Table 4 provides the recommended carbohydrate intake in each protocol.

The amount of correction insulin to administer to reduce ketosis also varies among protocols (Table 4). The STOP DKA protocol has by far the most specific system for calculating a correction bolus dose and provides specific insulin recommendations based on blood glucose and ketone levels. Comparatively, the STICH protocol recommends that patients take 1.5 times their usual dose, the International Consensus protocol states that the bolus should be based on carbohydrate intake, and EMA guidance simply states that extra rapid-acting insulin is needed. The recommended timing of additional correction insulin and carbohydrates and the frequency of ketone and glucose level checks during ketosis/DKA also differ slightly among protocols. If high ketone levels are present (>3.0 mmol/L) or symptoms persist, patients are advised to seek professional medical attention.

Hospital Treatment of DKA

There is a lack of published medical literature regarding the appropriate hospital protocol for SGLT2 inhibitor–induced DKA. Case studies have shown that DKA related to SGLT2 inhibitor therapy may result in glycosuria for at least 3 days after hospital admission in patients with either type 1 or type 2 diabetes (27). There was also a concomitant increased risk of DKA relapse in these patients. In comparison, research on classic DKA in type 1 diabetes has shown resolution of the condition in ~11 hours (28), suggesting that there may be mechanistic differences between the two types of ketoacidosis or that the drug requires more time to clear.

The FDA recently approved a label update stating that canagliflozin, dapagliflozin, and empagliflozin when used as an approved treatment for type 2 diabetes should each be discontinued at least 3 days before scheduled surgery, but this guidance also has implications for those with type 1 diabetes who use the therapy off-label (29). If hospitalization is necessary, standard DKA treatment protocols should be followed, with careful monitoring of ketones. Special care should be taken to provide enough insulin and carbohydrates to clear ketones. When a patient starts eating food, carbohydrates plus subcutaneous insulin are required. A carbohydrate-restricted hospital diet is not appropriate.

Discussion

Barriers and Potential Solutions

A number of existing barriers, as evidenced in the various protocols, prevent greater usage of this class of drugs.

TABLE 3 Consideration for Management of SGLT2 Inhibitor Use

	STICH (20)	International Consensus (18)	STOP DKA (19)	Anne L. Peters' Protocol (14)	EMA Guidance (11,12)	NICE Guidance (21–23)
Blood vs. urine ketone monitoring	Both are acceptable, although blood monitoring is more accurate	• Blood monitoring preferred • Urine monitoring is acceptable if blood monitor not accessible/affordable	Only blood monitoring	Either blood or urine monitoring	Either blood or urine monitoring	NA
Frequency of routine ketone checks	Routine	• As a matter of routine, but individualized to the patient • Random or periodic measurements recommended	NA	Every morning initially and then as needed based on symptoms or changes in habits and every 1–2 hours to track resolution of ketones if elevated	Individualized	NA
When to hold SGLT2i	24 hours in advance of occurrences that cause decreased insulin dose (e.g., surgery, fasting, reduced carbohydrate intake, or prolonged physical activity)	• For increased physical activity • In situations where the person may become dehydrated, alter dietary intake, or consume more alcohol than usual	At least 3 days before major surgery	Hold SGLT2i for anything out of the ordinary (e.g., marked increase in physical activity, physical illness, any procedures, fasting, going on a diet, feeling sick, or travel)	NA	NA

SGLT2i, SGLT2 inhibitor.

Starting with patient selection, patients require access to knowledgeable, trained, and readily available medical professionals who can recognize and deal with ketosis and potential DKA. Patients often present to the emergency department of their local hospital with symptoms that are not readily associated with DKA, especially if their glycemic levels are normal or only slightly elevated; this situation can be extremely dangerous or life-threatening, even in the hospital setting. Patients taking SGLT2 inhibitors are advised to carry wallet cards with information about DKA, but these materials may not be remembered in the whirlwind of an emergency, and greater education for patients, patients' families, and HCPs is required. Mandated education programs potentially could be implemented when patients pick up their prescriptions after regulatory approval is obtained for use of SGLT2 inhibitors in patients with type 1 diabetes.

In addition to issues of patient selection, the protocols themselves can be difficult to navigate due to many of the intricacies described above. For example, although the STOP DKA protocol is extremely helpful in its specificity regarding correction insulin dosages, calculations based on specific blood glucose and ketone levels can be cumbersome for patients and HCPs to use. The development of a digital application that could automatically provide a recommended dose with the input of blood glucose and ketone values could facilitate this process.

Furthermore, a survey of 161 specialists regarding off-label use in Italy showed that 45% used SGLT2 inhibitors off-label, but only some used International Consensus recommendations to reduce DKA risk, and two-thirds believed that ketosis required blood glucose levels >200 mg/dL (30).

As with many treatments, cost is another barrier to broader uptake. The costs of a blood ketone monitor and its necessary strips can add up over time, adding to the baseline cost for the SGLT2 inhibitor itself. As CGM technology and access improves, we hope to see systems that will incorporate ketone levels into this highly efficacious piece of diabetes technology.

This discussion has focused on protocols for prescribing SGLT2 inhibitors for people with type 1 diabetes. In the United States, SGLT2 inhibitors are not FDA-approved for this use, and thus most patients receiving these medications have type 2 diabetes. DKA, although more frequent in those with type 1 diabetes, is also occasionally reported in patients with type 2 diabetes. It is important to be aware that any patient with diabetes who is being treated with an SGLT2 inhibitor may develop DKA with near-normal blood glucose levels. Therefore, all HCPs should measure blood ketones and conduct other appropriate tests for DKA in those taking SGLT2 inhibitors who are acutely ill. Also, it may be prudent to discuss the possibility of DKA and its

TABLE 4 Considerations for Management of Ketosis/DKA

	STICH (20)	International Consensus (18)	STOP DKA (19)	Anne L. Peters' Protocol (14)	EMA Guidance (11,12)	NICE Guidance (21–23)
Stages of ketonemia/DKA by ketone level (BHB), mmol/L, or ketonuria	• >3.0 or significant ketonuria (more than ++): DKA	• 0.6–1.5 or trace/small/+ urine reading: ketonemia • 1.6–3.0 or moderate/++ urine reading: impending DKA • >3.0 or large/very large/+++/++++: probable DKA	• <1.0: normal or mild • 1.0–1.4: moderate • 1.5–2.9: high • ≥3: extreme	• 0.6 mmol/L: ketonemia	• 0.6–1.5 or trace/small/+ urine reading: ketonemia • >1.5–3.0 or moderate/++ urine reading: impending DKA • >3.0 or large/very large/+++/++++ urine reading: probable DKA	NA
Other measures of DKA	• Blood glucose >200 mg/dL • Bicarbonate <15.0 mmol/L • Venous pH <7.3	NA	NA	NA	NA	NA
Stopping SGLT2i	When high ketones are detected, stop SGLT2i for a few days	When elevated ketones are present, discontinue SGLT2i until ketones are back to baseline	Stop SGLT2i when DKA symptoms (lethargy, loss of appetite, nausea, abdominal pain) are present	If any signs/symptoms of physical illness occur, stop SGLT2i and test ketones	• Stop SGLT2i if BHB >1.5 mmol/L or at moderate/++ urine ketone reading • Stop SGLT2i if ketone levels persist and symptoms are still present with ketonemia	• Assess A1C after 6 months and regularly thereafter; if no sustained improvement in glycemic control (>0.3% drop in A1C), stop dapagliflozin • Stop at eGFR consistently <40 mL/min/1.73 m^2
Carbohydrate and fluid intake	• 30–60 g carbohydrates • 200–500 mL fluids hourly	• Ketonemia: 15–30 g carbohydrates; 300–500 mL fluids hourly • Impending DKA: same as above; also consider seeking medical attention • Probable DKA: seek immediate medical attention	• 30–60 g carbohydrates • 200–500 mL fluids hourly • Also depends on blood glucose	• If ketones >0.6 mmol/L, increase carbohydrate intake, give more insulin, drink fluids, and hold SGLT2i until back to baseline • Monitor until ketones return to normal	• Patient may need to drink water • Extra carbohydrates should be taken if blood glucose is normal or low	NA

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TABLE 4 Considerations for Management of Ketosis/DKA

	STICH (20)	International Consensus (18)	STOP DKA (19)	Anne L. Peters' Protocol (14)	EMA Guidance (11,12)	NICE Guidance (21–23)
Correction insulin	1.5 times the usual dose	Based on carbohydrate intake	• Moderate or higher ketones: consider increasing basal insulin by 20–50% until return to baseline • Calculate specific correction bolus insulin based on blood glucose and ketone level or use daily dosage calculation based on Table 6B in the STOP DKA report (19)	See description in text; give carbohydrates + correction dose; 1.5 times the usual correction dose if >200 mg/dL	Need to take extra rapid-acting insulin	NA
Frequency of additional correction insulin and carbohydrates	Every 1–2 hours	Every hour	Every 2–4 hours	Every 1–2 hours	NA	NA
Frequency of ketone checks during ketosis/DKA	Every 2–4 hours	If BHB >0.6 mmol/L, every 3–4 hours until resolution	Every 2–4 hours	Every 1–2 hours	2 hours after initial check	NA
Frequency of glucose checks during ketosis/DKA	NA	Frequently	Every 2–4 hours	Every 1–2 hours with ingestion of carbohydrates and fluids	Check glucose levels frequently to avoid hyperglycemia or hypoglycemia	NA
When to seek medical attention	• Ketone levels >3.0 mmol/L, any management steps cannot be followed, or ketonemia does not resolve in 4–6 hours • If there are symptoms of DKA, including abdominal pain, nausea, vomiting, fatigue, and/or dyspnea	• At "probable DKA" BHB or urine reading • If DKA symptoms and/or ketones are worsening	• If high levels of ketones persist despite extra insulin and/or increased carbohydrate intake over a period of 6–10 hours • If vomiting • If unable to keep down fluids • If there are persistent symptoms of DKA	• If unable to keep down fluids, go to emergency department; otherwise, contact HCP if ketones are increasing and not responding to treatment within 1–2 hours • Always contact HCP if in doubt	>3.0 or large/very large/+++/++++ urine reading	NA

SGLT2i, SGLT2 inhibitor.

common symptoms with all patients who receive an SGLT2 inhibitor prescription.

Ongoing Research Questions

Our survey of the protocols revealed a number of research questions that would benefit from further investigation. Do any of these protocols actually reduce DKA risk? If so, by how much? Also, all of the questions about ideal patient characteristics, as well as best methods and frequency of ketone testing, remain to be answered by future research. The questions of whether implementation of any of these protocols improves blood ketone levels and the rate at which patients with type 1 diabetes develop ketosis or DKA have not yet been validated.

In terms of SGLT2 inhibitor safety research, is the rate of DKA with SGLT2 inhibitors dose dependent? How relevant a precaution is the minimum insulin dose requirement, which is only seen in NICE guidance? Is the BMI cut point found in the EMA and NICE guidance effective in reducing DKA? Can SGLT2 inhibitors be prescribed to those with an A1C >10.0%? Does insulin resistance increase or decrease the DKA rate?

Pivoting to DKA risk management, what is the optimal frequency of routine ketone monitoring? Should blood ketones be required rather than urine ketones? How frequently should blood ketones and blood glucose levels be tested during potential DKA? Broadly, is A1C the best metric for assessing the success of SGLT2 inhibitors in the case of economic modeling? What about weight, time in range, or time in hypoglycemia?

All of these questions require further elucidation.

Conclusion

From our review of the various protocols, it is abundantly clear that SGLT2 inhibitors are a challenging class of drugs to safely implement in type 1 diabetes, and DKA risk mitigation must be systematically pursued because, for now, it is more of an art than a science. Given the ongoing need for adjunctive therapies in type 1 diabetes and current usage of the therapy worldwide, further education, research, and innovations will be crucial moving forward. In particular, hospital treatment of DKA is an area that could benefit greatly from further education and investigation. Although more research is needed to provide definitive answers, it may be prudent to prescribe SGLT2 inhibitors only for motivated patients with type 1 diabetes who have a BMI >27 kg/m^2, are not following a carbohydrate-restricted diet, have daily insulin use >0.5 units/kg/day, are willing to measure ketones and understand the meaning of their levels, have baseline ketones <0.6 mmol/L, and have a baseline A1C <9.0%.

DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

R.T. wrote the manuscript and researched the data. M.K. and C.M.A. reviewed/edited the manuscript. K.L.C., J.B.B., and A.L.P. contributed to revisions of the manuscript. C.M.A. is the guarantor of this work and, as such, had full access to all the data reviewed and takes responsibility for the integrity of the review.

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