Sodium glucose cotransporter 2 inhibitor-induced ketoacidosis is unlikely in patients without diabetes

Sodium glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, dapagliflozin, ertugliflozin and canagliflozin, increase urinary excretion of glucose by inhibiting reabsorption from renal proximal tubules. Glycaemic, cardiovascular and renal benefits of SGLT2 inhibitors have propelled their popularity. They are an established treatment for type 2 diabetes, heart failure with reduced or preserved ejection fraction, and chronic kidney disease, irrespective of diabetes status.[1-7]

Diabetic ketoacidosis is a rare but serious adverse event associated with SGLT2 inhibitor use in individuals with type 2 diabetes.[1,2] This rare adverse event has led to guidelines that recommend withholding the medication in the presence of low carbohydrate diets or excessive alcohol intake, if fasting for a procedure, or if unwell with active infection.[8] Most guidelines do not distinguish between patients with and without diabetes, as SGLT2 inhibitors were initially approved for the treatment of type 2 diabetes. These guidelines have led to delay of some procedures when patients have not withheld their SGLT2 inhibitors before surgery.

SGLT2 inhibitor-induced diabetic ketoacidosis is postulated to be caused by increased glucagon relative to insulin, leading to lipolysis and excess free fatty acid production with increased hepatic ketogenesis. In diabetes, or pre-diabetes, there is a relative or absolute insulin deficiency, which contributes to this process. Individuals without diabetes secrete adequate insulin, which is protective and, as such, ketoacidosis is not generally described.

SGLT2 inhibitors increase renal reabsorption of ketones and, thus, urinary ketone measurement may be uninformative. Blood ketone measurement is the investigation of choice if diabetic ketoacidosis is suspected.[8] Asymptomatic elevations in ketone levels have been observed in patients with type 2 diabetes taking SGLT2 inhibitors. There is speculation that mild ketosis contributes to the cardiac and renal benefits of SGLT2 inhibitor use.

Ketosis can occur in other settings, such as prolonged fasting or excessive alcohol use, but this rarely results in acid-base disturbances. Fasting ketosis (up to 1.7 mmol/L) can occur in patients without diabetes and not exposed to SGLT2 inhibitors, as demonstrated before colonoscopy.[9] Ketosis without acidosis can cause nausea, which can contribute to poor caloric intake and further exacerbate ketosis. Monitoring of ketones should be considered in patients who are clinically unwell, especially if exposed to SGLT2 inhibitors, as dextrose infusion can improve clinical outcome.

In large placebo-controlled trials of SGLT2 inhibitors for the treatment of type 2 diabetes, diabetic ketoacidosis was identified as a notable adverse event (Box).[1,2] Outside of clinical trials, diabetic ketoacidosis risk with SGLT2 inhibitor use has been reported to be higher.[10] This is based on data using the Food and Drug Administration Adverse Event Reporting System database or insurance claim databases, with limited details about the individual cases.[10]

In the large placebo-controlled trials of SGLT2 inhibitors for heart failure, there have been no reported cases of ketoacidosis in patients without diabetes (Box).[3-6] However, protocols specified that investigators should consider temporarily discontinuing trial medication in clinical situations known to predispose to ketoacidosis.[4,5] Whether this advice was followed, or how often, was not reported. It is feasible that this may have protected

Rates of diabetic ketoacidosis in sodium glucose cotransporter 2 (SGLT2) inhibitor trials stratified by diabetes status

	SGLT2 inhibitor		Placebo	
Trial	Diabetes	No diabetes	Diabetes	No diabetes
EMPA-Kidney[7]	5/1525 (0.3%)	1/1779 (0.1%)	1/1515 (0.1%)	0/1790
EMPA-Reduced[4]	0/927	0/936	0/929	0/934
EMPA-Preserved[5]	4/1466 (0.3%)	0/1531	5/1472 (0.3%)	0/1519
EMPA-REG[1]	4/4687 (0.1%)	na	1/2333 (<0.1%)	na
DECLARE-TIMI 58[2]	27/8574 (0.3%)	na	12/8569 (0.1%)	na
DAPA-HF[3]	3/993 (0.3%)	0/1380	0/990	0/1381
DELIVER[6]	2/1401 (0.1%)	0/1730	0/1405	0/1727
Overall rate	45/19 573 (0.2%)	1/7356 (< 0.1%)	19/17 213 (0.1%)	0/7351 (0.0%)

na = not applicable. ◆

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against some events. Interestingly, the EMPA-KIDNEY trial reported a single case of ketoacidosis in an individual apparently without diabetes treated with empagliflozin, but further details of this case are not available.[7] To date, there are no reported cases of SGLT2 inhibitor-induced ketoacidosis with confirmed elevation of blood ketones occurring in patients without diabetes outside a clinical trial setting.

As diabetes status appears important in stratifying risk of ketoacidosis with SGLT2 inhibitors, it must be noted that globally 14.7–58.8% of individuals with diabetes remain undiagnosed.[11] Hence, it is likely that many individuals who commence treatment with SGLT2 inhibitors may have underlying undiagnosed diabetes or pre-diabetes. Vigilance in screening for diabetes before commencing SGLT2 inhibitors is important. With scarcity of data, the risk–benefit profile and potential costs of unnecessary testing is unknown.

In conclusion, pharmacovigilance is critical to determine if the near-zero risk of ketoacidosis in patients without diabetes in large clinical trials translates to real world experience. Theoretically, the risk of ketoacidosis in a patient without diabetes should be negligible. However, the risk can be minimised with increased awareness. Undiagnosed diabetes may explain such cases and should be actively excluded before commencing an SGLT2 inhibitor. As SGLT2 inhibitors are increasingly used, additional experience will help to determine the risk of ketoacidosis in patients without diabetes. Guidelines may need to be updated to differentiate between patients with and without diabetes to avoid unnecessary investigations and, potentially, deferment of surgery if the apparently negligible risk of ketoacidosis in clinical trials eventuates in clinical practice.

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