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ADVERSE DRUG REACTIONS

Diabetic ketoacidosis with SGLT2 inhibitors

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What you need to know

- Sodium-glucose cotransporter-2 (SGLT2) inhibitors are relatively new drugs approved for diabetes, but they increase the risk for diabetic ketoacidosis, particularly in patients with type 1 diabetes and those with certain high risk conditions
- In some cases blood glucose levels are normal or only mildly elevated, a condition known as euglycaemic ketoacidosis, which can delay the diagnosis
- Check ketones in patients taking SGLT2 inhibitors with symptoms or precipitating factors for ketoacidosis regardless of blood glucose levels

A 45 year old woman with type 2 diabetes complains of malaise, shortness of breath, and nausea for two days. She has been taking metformin and insulin. She was started on canagliflozin six weeks earlier to improve glycaemic control. Over the previous week she has halved the insulin dose. On examination, she is drowsy. Her respiratory rate is 28 breaths/min with a deep breathing pattern. A random blood glucose test shows 8 mmol/L (144 mg/dL). Blood tests reveal metabolic acidosis with an increased anion gap of 23 mmol/L (reference range 8-12 mmol/L), pH 7.18, and bicarbonate 14 mmol/L. Urine dipstick showed ketones +++.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, used in patients with diabetes, can cause diabetic ketoacidosis. This is rare but can be serious and life threatening. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) warn about possible "atypical" presentation of diabetic ketoacidosis with SGLT2 inhibitors[1 2]: instead of having hyperglycaemia, patients may have normal or only mildly elevated blood glucose levels (<13.9 mmol/L, <250 mg/dL). This may delay diagnosis. In 2020, the FDA and EMA updated guidance to interrupt SGLT2 inhibitors and monitor ketosis in patients scheduled for surgery or hospitalised.[3 4]

What are SGLT2 inhibitors?

SGLT2 inhibitors, also called gliflozins, lower blood sugars by causing kidneys to remove glucose from the body in urine.[5] Figure 1 depicts their actions. They are used as second or third line therapy in type 2 diabetes along with metformin, sulfonylurea, or insulin to improve glycaemic control.[6] In 2019, consensus guidelines in the US and Europe further recommended their use in patients with type 2 diabetes and established cardiovascular disease or chronic kidney disease.[5 7] SGLT2 inhibitors represented 14% of new second line prescriptions and 27% of new third line prescriptions for type 2 diabetes in primary care in the UK in 2016.[8]

This is one of a series of occasional articles to help doctors prevent, diagnose, and respond to adverse drug reactions that may be serious if not recognised. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and City Hospital Birmingham, and Patricia McGettigan, reader in clinical pharmacology and medical education, Queen Mary University of London.

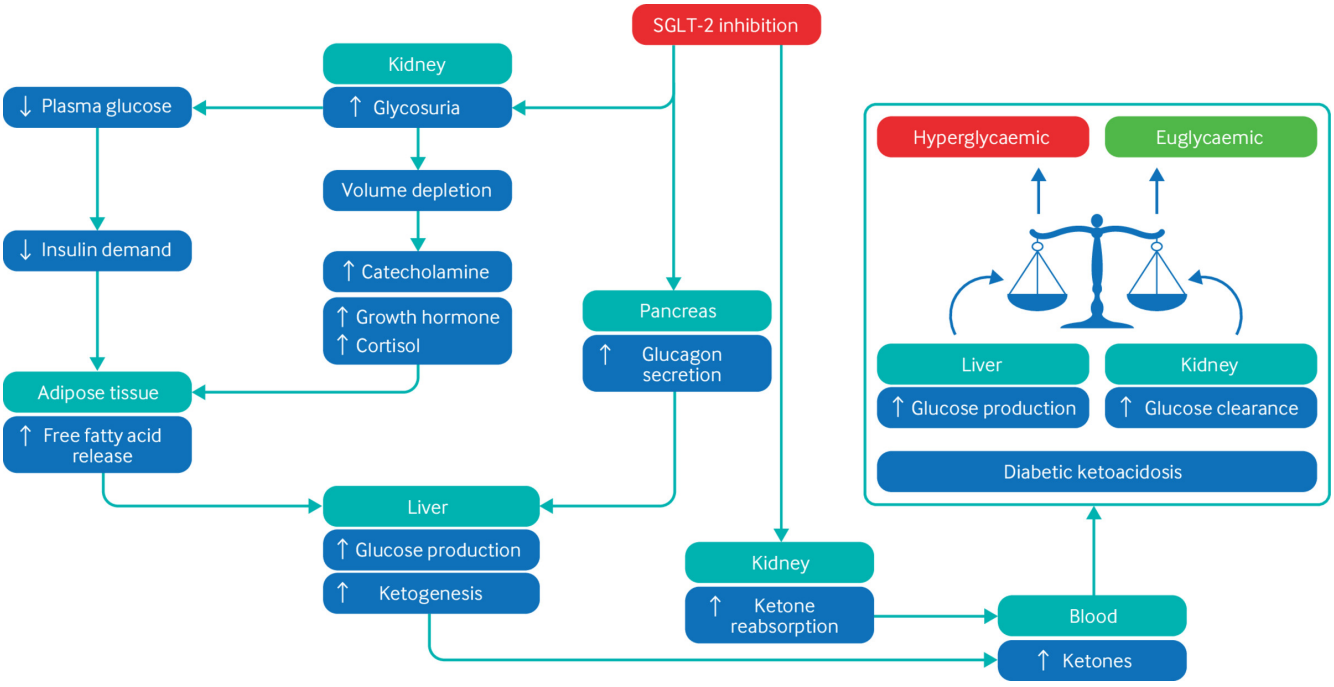

Fig 1 | Actions of SGLT2 inhibitors in ketoacidosis. SGLT2 inhibitors inhibit SGLT2 on pancreatic islet α-cells and directly stimulate glucagon secretion, which up-regulates endogenous glucose production, ketogenesis, and lipolysis. In the kidney, SGLT2 inhibition increases ketone reabsorption. SGLT2 inhibition-induced glycosuria lowers blood glucose, thereby allowing insulin dose reduction. Insulin reduction further reduces the insulin:glucagon ratio, a critical factor in inhibiting hepatic ketogenesis and lipolysis of free fatty acids. Glycosuria also induces osmotic diuresis and dehydration, which triggers the synthesis of glucagon, cortisol, and adrenaline, further contributing to lipolysis and ketogenesis

Few SGLT2 inhibitors have been approved for type 1 diabetes in Europe and Japan as an adjunct to insulin to improve glycaemic control. The FDA has rejected their use in type 1 diabetes because of a higher risk of diabetic ketoacidosis in these patients.[9 10] Supplementary table 1 on bmj.com lists indications and licensing for SGLT2 inhibitors.

How do patients with this adverse reaction present?

Symptoms of diabetic ketoacidosis include excessive thirst, frequent urination, dehydration, nausea, vomiting, abdominal pain, shortness of breath, and altered sensorium.[11-14] Patients may report malaise, dizziness, and syncope, with or without fever, which are non-specific.[15]

Diabetic ketoacidosis is typically characterised by hyperglycaemia. Over a third of patients with ketoacidosis associated with SGLT2 inhibitor have normal or only mildly elevated blood glucose levels (<13.9 mmol/L, <250 mg/dL), also referred to as euglycaemic diabetic ketoacidosis.[16 17] In such cases, the absence of hyperglycaemia and the less severe polyuria polydipsia, owing to the milder degree of hyperglyacemia-induced osmotic diuresis, can delay diagnosis.[1 15 18]

How common is this adverse reaction?

The relative risk of diabetic ketoacidosis is higher in patients with type 1 diabetes. Observational studies with SGLT2 inhibitors suggest an incidence of 1.3-8.8 ketoacidosis events per 1000 patient-years in type 2 diabetes[19-22] and 7.3 events per 1000 patients-years in type 1 diabetes.[23] The risk is higher in the first few months of initiating treatment. Between 76.8% and 85.2% of ketoacidosis events occur within 180 days of starting SGLT2 inhibitors in observational studies and pharmacovigilance reports.[15 22 24]

What is the evidence?

Supplementary table 2 on bmj.com lists epidemiological evidence linking diabetic ketoacidosis to SGLT2 inhibitors. In an analysis of 487 cases of ketoacidosis from the WHO pharmacovigilance database, ketoacidosis was more frequently reported with gliflozins than with other glucose-lowering drugs (adjusted reporting odds ratio 15.5 (95% confidence interval 12.8 to18.7).[25]

A meta-analysis of 13 randomised controlled trials (5397 patients) found that SGLT2 inhibitors increased the risk of diabetic ketoacidosis in type 1 diabetes (risk ratio 4.49 (95% CI 2.88 to 6.99))[15] in a dose dependent manner, with a 4.9-fold higher rate at high doses of SGLT2 inhibitors (34 events per 1000 patient-years) than with low doses (7 events per 1000 patient-years). Sotagliflozin was associated with an increased risk of ketoacidosis in type 1 diabetes (relative risk 3.93 (1.94 to 7.96)) compared with placebo in a meta-analysis (6 RCTs, 3238 patients)[16]: higher baseline HbA1c was associated with a lower risk of diabetic ketoacidosis, and the magnitude of basal insulin dose reduction was associated with an increased risk of diabetic ketoacidosis.

High quality evidence from a systematic review and meta-analysis (39 RCTs, 60 580 patients) suggests an increased risk of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes compared with placebo or other antidiabetic drugs (relative risk 2.13 (1.38 to 3.27)), with an absolute rate of 3 events per 1000 patient-years.[26]

What factors increase the risk?

Certain conditions predispose to diabetic ketoacidosis (box 1, supplementary table 3). Over two thirds of patients who develop diabetic ketoacidosis are noted to have one of these factors in observational studies of SGLT2 inhibitors.[20 24 27]

Box 1: Predisposing conditions and precipitating factors of diabetic ketoacidosis in patients taking SGLT2 inhibitors

Predisposing condition

- Inability or unwillingness to monitor ketone bodies
- Excessive alcohol use or illicit drug use
- Very low carbohydrate or ketogenic diet
- Pregnancy (ongoing or planned)
- Previous diabetic ketoacidosis
- Inappropriate insulin dose reduction
- SGLT2 inhibitor dose
- Insulin pump use
- Late-onset autoimmune diabetes of adulthood (LADA)

Precipitating factor

- Vomiting
- Volume depletion or dehydration
- Acute infection or illness of any sort
- Hospitalisation for surgery or acute serious medical illness
- Acute volume depletion or dehydration
- Vigorous or prolonged exercise
- Insulin pump or infusion site failure
- Travel with disruption in usual schedule or insulin regimen

How is it diagnosed?

Test patients with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level.[1 -3] The following findings indicate ketoacidosis[11 -14]:

- *Increased ketones* in blood (β-hydroxybutyrate ≥3 mmol/L) or urine (ketonuria ++ or higher on urine dipsticks). Blood ketone testing is preferred over urine test strips as it is more accurate for detecting onset and resolution of ketosis[28]
- *Acidosis*—serum bicarbonate <15 mmol/L and/or blood pH <7.3. An elevated serum anion gap (sum of serum chloride and bicarbonate concentrations subtracted from the serum sodium concentration) >10 mmol/L may help rule out other causes of metabolic acidosis if blood ketone testing is unavailable.[7]

Once ketoacidosis is diagnosed, other conditions that can cause it, usually in the form of euglycaemic ketoacidosis, should be excluded. These conditions and hints for differential diagnosis are listed in supplementary table 4.

How is it managed?

In patients with suspected or confirmed ketoacidosis, stop SGLT2 inhibitors immediately. International consensus guidelines for type 1 diabetes recommend the STICH protocol (stop SGLT2 inhibitor, inject bolus insulin, consume 30 g carbohydrates, hydrate)[29] and the STOP diabetic ketoacidosis protocol (stop SGLT2 inhibitor, test ketones, oral ingestion of fluid and carbohydrates, protocol instructions for supplemental insulin and carbohydrates)[30] (see supplementary table 5 for details). Early initiation of these measures can reverse ketosis and prevent progression to diabetic ketoacidosis.[16 24]

Avoid restarting SGLT2 inhibitors after an episode of ketoacidosis unless another cause is clearly identified and resolved.[2] Even so, patients remain at risk of recurrence with SGLT2 inhibitors, and other antidiabetic drugs are preferred.[17 24]

How can the risk of harm be minimised?

Assess patients for risk factors for ketoacidosis and avoid prescribing SGLT2 inhibitors in these patients (box 1, supplementary table 3).[6 13] Explain the risk of ketoacidosis to patients before starting treatment. Start with the lowest dose required for clinical benefit. Explain when and how to measure ketones and actions to take if ketones are elevated. Patients must regularly monitor ketones in the initial weeks of therapy, regardless of symptoms.[18] SGLT2 inhibitors are better avoided in patients unable to monitor ketones. Later, individualise the frequency of ketone testing according to each patient's lifestyle and risk factors. Avoid insulin dose reduction and ask patients to check ketones with every change in insulin pump set and insulin dose. Stop SGLT2 inhibitors during acute serious medical illness and at least three days before scheduled surgery and monitor ketones after drug interruption (supplementary table 3).

Ask the patients to check ketones if they develop symptoms or precipitating factors for ketoacidosis. If ketones are elevated, they should hold the medication and promptly consult their doctor.[29 30]

Sources and selection criteria

We searched PubMed, EMBASE, Cochrane Database of Systematic Reviews, international trial registries, and drug regulatory agencies' websites up to 15 July 2020 using the search terms "ketoacidosis, diabetic, DKA, euglycemic diabetic ketoacidosis, euDKA, ketone, ketosis, acidosis, sodium glucose cotransporter 2 (SGLT2) inhibitors." We prioritised articles on humans, scientific society guidelines (ADA, EASD, ESC, NICE, British Diabetes Societies), expert reviews, and articles providing mechanistic insights into diabetic ketoacidosis. We included in our analysis 307 records (13 systematic reviews, 161 RCTs, 30 records from regulatory agencies,13 consensus/guidelines 59 case series, and 31 reviews on SGLT2 inhibitor-associated diabetic ketoacidosis).

Education into practice

- When do you start a patient on sodium-glucose cotransporter-2 (SGLT2) inhibitors? What factors do you consider when choosing these drugs?
- How would you discuss the risk of diabetic ketoacidosis with a patient when starting SGLT2 inhibitors and strategies to minimise the risk?
- How do patients at your practice prescribed SGLT2 inhibitors adhere to measuring ketones?

How patients were involved in the creation of this article

We arranged a live Tweet chat with 12 patients with type 2 diabetes taking SGLT2 inhibitors for their views on an initial draft of this article. Patients emphasised that general physicians educate patients on strategies to minimise the risk for diabetic ketoacidosis and the need for providing a blood ketone meter to patients taking SGLT2 inhibitors. Based on their feedback we now highlight the importance of checking ketone levels if patients have predisposing conditions and precipitating factors for diabetic ketoacidosis, irrespective of symptoms. We are grateful for their input.

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Patient consent: Not required (patient anonymised, dead, or hypothetical).

Provenance and peer review: Commissioned, based on an idea from the author; externally peer reviewed.

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