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Diabetic ketoacidosis with SGLT2 inhibitor use – a patient series

SHORT REPORT

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BACKGROUND

Inhibitors of sodium glucose cotransporter 2 (SGLT2 inhibitors) are increasingly being used to treat type 2 diabetes. Results from previous studies suggest a rising incidence of diabetic ketoacidosis with the use of this medication.

MATERIAL AND METHOD

We performed a diagnosis search in the electronic patient records at Haukeland University Hospital for the period 1 January 2013–31 May 2021 with the aim of identifying patients with diabetic ketoacidosis who used SGLT2 inhibitors. A total of 806 patient records were reviewed.

RESULTS

Twenty-one patients were identified. Thirteen had severe ketoacidosis, and ten had normal blood glucose levels. Probable triggering causes were found in 10 of the 21, with recent surgery being the most common (n = 6). Three of the patients were not tested for ketones, and 9 were not tested for antibodies to rule out type 1 diabetes.

INTERPRETATION

The study showed that severe ketoacidosis occurs in patients with type 2 diabetes using SGLT2 inhibitors. It is important to be aware of this risk and the fact that ketoacidosis can occur without hyperglycaemia. Arterial blood gas and ketone tests must be performed to make the diagnosis.

Main findings

Thirteen of the 21 patients admitted to hospital with SGLT2 inhibitor-associated diabetic ketoacidosis were severe cases.

In 10 of the 21 patients with ketoacidosis, glucose levels were normal.

Three of the 21 patients were not tested for ketones, and 9 were not tested for antibodies to rule out type 1 diabetes.

Since their introduction in 2013, inhibitors of sodium glucose cotransporter 2 (SGLT2 inhibitors) have become a common treatment for type 2 diabetes (1). They have been shown to reduce cardiovascular mortality in this patient group and delay the progression of chronic kidney disease (2). However, several cases of diabetic ketoacidosis have been reported in patients with type 2 diabetes, also with normal blood glucose levels (3, 4).

Diabetic ketoacidosis is a life-threatening catabolic condition resulting from insulin deficiency. The criteria for the condition are serum glucose above 11.1 mmol/L, ketones in the blood above 3.0 mmol/L and/or ketones in the urine corresponding to 2+ on a urinalysis, and metabolic acidosis (5). If the blood glucose level is within the normal range, euglycemic ketoacidosis is indicated.

The mechanism of such ketoacidosis has not been clarified. Several factors can be triggers, such as dehydration, hunger, alcohol, surgery, infection and other intercurrent diseases (5). SGLT2 inhibitors have a blood glucose-lowering effect, in which the reabsorption of glucose and sodium in the proximal renal tubules is inhibited (6) and insulin secretion is reduced. Inhibition of SGLT2 receptors in alpha cells stimulates glucagon secretion, which increases fat breakdown and the formation of ketones (2, 4). The medication also causes a loss of bicarbonate (7). Large reductions in the insulin dose when starting treatment with an SGLT2 inhibitor can also be a trigger (4, 8).

Clinical case studies suggest a possible connection between SGLT2 inhibitors and ketoacidosis (9, 10). Norway's regional medicines information and pharmacovigilance centres (RELIS) have received reports of 106 possible cases since 2015 (RELIS, personal communication). Experience in the area is limited, and there is an absence of specific treatment recommendations (3).

We wanted to map the incidence and clinical course of ketoacidosis in patients using SGLT2 inhibitors who were admitted to Haukeland University Hospital in the period 2013–21.

Material and method

Patients with type 2 diabetes treated with SGLT2 inhibitors admitted to hospital with ketoacidosis in the period 1 January 2013–31 May 2021 were identified retrospectively via a diagnosis search for the Medical Department, Surgical Department and Cardiovascular Department at Haukeland University Hospital. Relevant diagnostic codes were E11.0 (type 2 diabetes with hyperosmolar or hypoglycaemic coma, with or without ketoacidosis) and E11.1 (type 2 diabetes with ketoacidosis without information on coma). We reviewed medical records manually in order to verify the diagnoses of type 2 diabetes and ketoacidosis, and whether the patient was using SGLT2 inhibitors. We

carried out supplementary searches for the diagnostic codes E10.0 (type 1 diabetes in hyperosmolar or hypoglycaemic coma, with or without ketoacidosis) and E10.1 (type 1 diabetes with ketoacidosis without information on coma), in case of miscoding of diabetes type. Anaesthesiologists identified an additional five patients treated in one of the postoperative or intensive care units for perioperative SGLT2 inhibitor-associated diabetic ketoacidosis, where ketoacidosis was not coded in the patient record.

Background information and details of the diagnosis and treatment were obtained from electronic patient records and summary care records. The use of SGLT2 inhibitors and the course of ketoacidosis were studied in detail. Laboratory results are based on the last level reported in the medical record before or during the period of hospitalisation in question.

The study was approved by the local Regional Committee for Medical and Health Research Ethics (REK no. 125784). The committee found that the relevant patients should receive a letter giving them the opportunity to decline participation.

Results

Two of the authors (GU, SL) identified and reviewed 806 patient records, in which 21 patients met the criteria for diabetic ketoacidosis with SGLT2 inhibitor use (Table 1) (11). No one declined to participate. The search yielded 225 patients with E11.0 and 150 with E11.1, and a review of medical records identified 16 who met the criteria. Among the 426 patients with E10.0 and E10.1, we found no one with type 2 diabetes. Five patients were not coded with ketoacidosis at the time of discharge from the surgical department and were not intercepted in the medical record search.

Table 1

Demographics and characteristics of diabetes and diabetic ketoacidosis in 21 patients with type 2 diabetes and SGLT2 inhibitor-associated ketoacidosis at Haukeland University Hospital during the period 1 January 2013–31 May 2021.

	Number/median (range)
Women	11
Age	66 (34–88)
BMI	23.7 (20.6–29.1)
Duration of diabetes (years)	13 (< 1–42)
Age at start of treatment with SGLT2 inhibitors	58 (30–86)
Type of SGLT2 inhibitor	
Empagliflozin[1]	14
Dapagliflozin	7
Other oral antidiabetics	19

	Number/median (range)
Insulin	7
Number with positive diabetes-associated autoantibodies test	12
Number with positive C-peptide test	9
Long-term blood sugar (mmol/mol)	73 (35–106)
Number with recognised possible triggering cause of ketoacidosis[2]	10
Glucose level with ketoacidosis (mmol/L)	13,9 (7,7–40,0)
Euglycemic ketoacidosis	10
Level of blood ketones (mmol/L)	5,5 (0,6–6,7)
Number with a positive ketones in blood test	12
Number with a positive ketones in urine test	15
Urine ketone level	3+ (2+ to 3+)
Severity of ketoacidosis[3]	
Mild	3
Moderate	5
Severe	13

[1]Of the 14 who used empagliflozin, two used empagliflozin/metformin combined medication..

[2]Recognised associated triggering factors were surgical procedures, infection, nutritional problems and comorbidity such as cardiovascular disease.

[3]Mild ketoacidosis was defined as bicarbonate 15–18 mmol/L and/or pH 7.25–7.35, moderate ketoacidosis as bicarbonate 10–14 mmol/L and/or pH 7.00–7.24, severe ketoacidosis as bicarbonate < 10 mmol/L and/or pH < 7.00 (11).

Table 1 shows diabetes and medication use in the patients. Twelve patients were tested for diabetes-associated autoantibodies. None of these were positive. Seven patients were very poorly regulated, with a long-term blood sugar level above 75 mmol/mol, while only two patients had satisfactory long-term blood sugar levels below 58 mmol/mol. Potential triggering causes were found in 10 of the 21 patients: surgical procedures (n = 6), infection (n = 2), nutritional problems (n = 1) and acute cardiovascular disease (n = 1). Three patients had mild ketoacidosis (bicarbonate 15–18 mmol/L and/or pH 7.25–7.35), while 13 had severe ketoacidosis (bicarbonate < 10 mmol/L and/or pH < 7.00). Ten patients were euglycaemic. Fifteen patients tested positive for ketones in the urine and 12 tested positive for ketones in the blood, while three were not tested for ketones. None of the patients died during their period of hospitalisation.

Discussion

Diabetic ketoacidosis in patients using SGLT2 inhibitors can easily be overlooked when the patient must have neither hyperglycaemia nor type 1 diabetes. Only 7 % of patients with diabetic ketoacidosis have euglycaemia (12). Both we and others have found a higher proportion of euglycaemia in SGLT2 inhibitor-associated diabetic ketoacidosis (4, 12, 13), and this has been reported to delay the diagnosis (4, 14). Testing for arterial blood gas and ketones in the blood and/or urine is therefore crucial for a quick and accurate diagnosis (15).

Studies show that patients treated with insulin have the lowest risk of SGLT2 inhibitor-associated diabetic ketoacidosis. An important part of emergency treatment is the administration of insulin (4, 10). One study found that 2 out of 13 patients had type 1 diabetes that was incorrectly classified as type 2 diabetes (14). We did not find any such cases, but almost half received no testing for antibodies. There is no recommendation on antibody testing when prescribing SGLT2 inhibitors, but it may be appropriate to recommend it for vulnerable groups, such as older patients and patients with nutritional problems. Most of our patients were admitted to hospital less than one year after starting treatment with SGLT2 inhibitors. Other research indicates that the risk is greatest in the early phase of treatment start-up (12).

Guidelines for temporary discontinuation of SGLT2 inhibitors in relation to acute illness, surgery and dehydration are described in the national guide for endocrinology (16). Several studies point to surgery as the most common triggering factor (4, 8, 14), and specific guidelines for surgery have been drawn up (17). Perioperative ketoacidosis is often treated in the postoperative or intensive care unit. In our experience, the diagnosis is not always coded at final discharge from the surgical department. If this is representative, the actual incidence may be higher than reported.

Conclusion

In the period 2013–21, we identified 21 patients with diabetic ketoacidosis who used SGLT2 inhibitors, ten of whom had normal glucose levels. It is important to be aware of the possibility of euglycaemic ketoacidosis in this patient group. Arterial blood gas and ketone tests must be performed where this is suspected.

The article has been peer-reviewed.

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