

## CASE STUDY

# Metabolic acidosis – expected and fatal adverse effects of metformin and empagliflozin: case series and literature review

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**DOI:** 10.21040/eom/2016.2.3.6

Received: August 21st 2016

Accepted: September 10th 2016

Published: September 15th 2016

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**Funding:** None.

**Conflict of interest statement:** The authors declare that they have no conflict of interest.

**Data Availability Statement:** All relevant data are within the paper.

## Abstract

Metformin, a well-known first-line diabetes therapy, and the recently developed sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin are widely used oral antihyperglycemic drugs in the long-term treatment of type 2 diabetes mellitus (T2DM). Metabolic acidosis is a potentially fatal adverse effect (AE) of these drugs with a high mortality rate. However, the reported incidence of metabolic acidosis in clinical practice has been proven to be very low. Nevertheless, it should be considered that the event rates are based on confounded data and spontaneous case reports.

Metformin increases plasma lactate levels by inhibiting mitochondrial respiration, which, accompanied by elevated plasma metformin concentrations (in renal impairment) and a secondary event that further disrupts lactate production (e.g., hypoperfusion, sepsis), typically leads to metformin-associated lactic acidosis (MALA).

At the same time, SGLT2 inhibitors are thought to promote ketogenesis and precipitate ketoacidosis by their extra-pancreatic glucuretic mode of action.

The present article describes 3 patients suffering from severe metabolic acidosis caused by metformin or empagliflozin, presents similar cases reported in the literature, and assesses the possible etiopathogenesis of the metabolic derangement. Diabetic patients should be educated about the importance of regular fluid and food intake as well as regular blood and urine glucose and ketone self-checkups, whereas physicians should be more aware that the key to an effective use of all glucose-lowering medication is appropriate patient selection, counseling, and follow-up. It is a good clinical sense which will ensure that physicians are able to translate pharmaceutical advances into clinical benefits for patients with T2DM.

**Patient consent:** The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, verbal and written informed consent has been obtained from the participants involved.

**Keywords:** type 2 diabetes mellitus; metformin; SGLT2 inhibitors; metabolic acidosis; renal insufficiencies; case reports

## 1. Introduction

Metformin remains the most commonly prescribed oral antihyperglycemic medication in the world and is considered the first-line therapy for newly diagnosed type 2 diabetes mellitus (T2DM) [1]. It is an oral biguanide antidiabetic agent which enhances the suppression of gluconeogenesis by insulin, reduces glucagon-stimulated gluconeogenesis, and increases the uptake of glucose by muscle and adipose cells [2].

The availability of a new class of glucose-lowering drugs, the sodium–glucose co-transporter 2 (SGLT2) inhibitors, has presented a major change in treatment options for T2DM. When compared with most standard oral agents, they appear to be similarly efficacious with regard to more potent HbA1c lowering. SGLT2 inhibitors act by inhibition of SGLT2 in the proximal nephron. Their mechanism of action reduces glucose reabsorption and increases glucose excretion by urine.

Although SGLT2 inhibitors are approved as monotherapy, they are mainly used in combination with metformin and/or other agents [1]. A rare but potentially fatal adverse effect (AE) associated with metformin and SGLT2 inhibitor use is metabolic acidosis.

Metformin-associated lactic acidosis (MALA) is uncommon. Its incidence is estimated of 0.03 to 0.06 per 1000 patient-years [2,3]. Estimates of the incidence of MALA are confounded by multiple factors. Data obtained from published trials, which typically exclude patients with risk factors for lactic acidosis and which are designed to provide standard of care, likely do not reflect actual rates in clinical practice [4,5]. Furthermore, information on plasma metformin concentrations, serum creatinine levels, arterial lactate levels, and history of concurrent pathologies is inconsistently reported, complicating the characterization of MALA vs. lactic acidosis of other etiologies [6]. Thus, the precise incidence of lactic acidosis in metformin users is not known, since event rates are very low and based on spontaneous case reports. Due to low event rates and spontaneous reports, accurate incidence of lactic acidosis caused by metformin is not well-known.

On June 12, 2015 the European Medicines Agency (EMA) announced that the Pharmacovigilance Risk Assessment Committee (PRAC) had started a review of all of the three approved SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) to evaluate the risk of diabetic ketoacidosis (DKA) in T2D (7). According to the EMA, as of May 2015 in EudraVigilance a total of 101 cases of DKA had been reported worldwide in T2D patients treated with SGLT2 inhibitors. Estimated exposure was over 0.5 million patient-years.

No clinical details were provided except for the mention that “all cases were serious and some required hospitalization. Even though DKA is typically associated with increased blood sugar levels, in many of these reports blood sugar levels were only moderately increased.

[7]. In February 2016, EMA’s PRAC finalized a review of SGLT2 inhibitors and established recommendations to minimize the risk of DKA [8].

Metformin and SGLT2 inhibitors are currently used in the management of T2DM worldwide and are commonly prescribed antidiabetic agents. Although high anion gap metabolic acidosis is a rare side effect of metformin and SGLT2 inhibitors, it may lead to potentially lethal complications.

The present paper describes three patients admitted to the Medical Intensive Care Unit (MICU) of the Sisters of Charity University Hospital Center (UHC), Zagreb, from January to February 2016, suffering from severe metabolic acidosis caused by metformin or empagliflozin.

Through the present case reports and literature review we aim to bring this complication to attention, describe its pathogenesis and contributing risk factors, and most importantly, emphasize the need for careful use in everyday practice.

## 2. Case reports

### 2.1. Patient 1

An 80-year-old male was admitted to the Emergency Department, Sisters of Charity UHC due to confusion, intermittent epigastric pain, nausea, vomiting, and diarrhea lasting for 2 weeks. Concomitant diseases and/or drugs at doses for possible drug interactions were not recorded.

The patient had a 5-year history of T2D treated with metformin. A month before admission, due to persisting high glucose levels, the previous metformin monotherapy (3 times 1,000 mg/ day) was replaced with alogliptin benzoate/metformin combination therapy (12.5/1,000 mg 2 times/day). Misunderstanding his physician, the patient continued taking his previous therapy together with the newly prescribed medication, which resulted in accidental metformin overdose. The drug was discontinued immediately after AE was suspected.

On admission, the patient was somnolent, tachypneic, with blood pressure 75/50 mmHg, heart rate 101 beats per minute, respiratory rate 31 per minute, and core body temperature 36.3 °C.

Initial laboratory investigations showed blood urea nitrogen 25.9 mmol/L, creatinine 703 μmol/L, sodium 145 mmol/L, potassium 6.5 mmol/L, chloride 104 mmol/L, glucose 26.6 mmol/L, and blood lactate 12.4 mmol/L. Arterial blood gas revealed severe wide anion gap acidosis (pH 6.91, pCO<sub>2</sub> 1.5 kPa, pO<sub>2</sub> 17.29 kPa, HCO<sub>3</sub><sup>-</sup> 2.2 mmol/L, base deficit -29 mmol/L).

The patient was admitted to the MICU and treated for acute kidney failure and hypovolemic shock with intravenous fluids, insulin, sodium bicarbonate, and inotropic agents.

Due to hemodynamic instability, continuous veno-venous hemodialysis (CVVHD) was performed with further intensive care medicine management. Four days after admission cardiorespiratory arrest occurred with fatal outcome.

### 2.2. Patient 2

A 77-year-old woman with T2D, on metformin (850 mg three times/day), was admitted to hospital for routine colonic polypectomy. Concomitant diseases and/or drugs at doses for possible drug interactions were not recorded.

A colonoscopy was performed and oral sodium phosphate (polyethylene glycol 3350 100 g, sodium sulfate 7.5 g, sodium chloride 2.69 g, potassium chloride 1.015 g, ascorbic acid 4.7 g, and sodium ascorbate 5.9 g in one liter) was used for bowel preparation. Metformin treatment was not stopped during the day of preparation for colonoscopy and the two days following colonoscopy. Since the colonoscopy revealed a polyp highly suspicious of malignancy, a CT scan with IV contrast was performed on the same day. The drug was discontinued immediately after AE was suspected.

The following day the patient presented with confusion, progressive dyspnea, nausea, and oliguria. She had no fever, blood pressure was 110/70 mmHg, heart rate 115 beats per minute, respiratory rate 23 per minute, and core body temperature 36.8 °C.

Laboratory investigations revealed acute renal failure with serum creatinine rising from 81 to 779 μmol/L in 3 days' time, sodium 133 mmol/L, potassium 5.7 mmol/L, chloride 98 mmol/L, glucose 11.9 mmol/L and blood lactate 10.8 mmol/L. Arterial blood gas showed severe wide anion gap acidosis (pH 6.93, pCO<sub>2</sub> 1.4 kPa, pO<sub>2</sub> 13.8 kPa, HCO<sub>3</sub><sup>-</sup> 2.2 mmol/L, base deficit -28.6 mmol/L).

The patient was transferred to the MICU and treated for MALA and acute renal failure with emergency hemodialysis and insulin. She recovered from acidosis and acute renal failure after four sessions of hemodialysis and was discharged on day 10. The patient was recommended to continue treatment with insulin.

### 2.3. Patient 3

A 62-year-old female with a history of T2D and hypertension was brought to the Emergency Department with fever, nausea, vomiting, and diarrhea lasting for 2 days.

Concomitant diseases and/or drugs at doses for possible drug interactions were not recorded.

Prior to hospitalization the patient was taking the SGLT2 inhibitor empagliflozin (25 mg/day) for T2DM. On admission, the patient had a body mass index of 27.2 kg/m<sup>2</sup>, her blood pressure was 150/80 mmHg, heart rate 120 beats per minute, respiratory rate 25 breaths per minute, and core body temperature 37.7°C. The drug was discontinued immediately after AE was suspected.

Initial investigations revealed blood urea nitrogen 8.4 mmol/L, creatinine 84 µmol/L, sodium 130 mmol/L, potassium 4.4 mmol/L, chloride 107 mmol/L, glucose 12.3 mmol/L, and blood lactate 0.9 mmol/L. Arterial blood gas showed metabolic acidosis (pH 7.12, pCO<sub>2</sub> 1.5 kPa, pO<sub>2</sub> 16.41 kPa, HCO<sub>3</sub><sup>-</sup> 3.6 mmol/L, base deficit -23.3 mmol/L). Urine analysis showed high levels of ketones (3+) and glucose (3+). A total blood count indicated leukocytosis with a shift to the left (WBC 15.2x10<sup>3</sup>, bands 80.5%), CRP was mildly elevated (15.2).

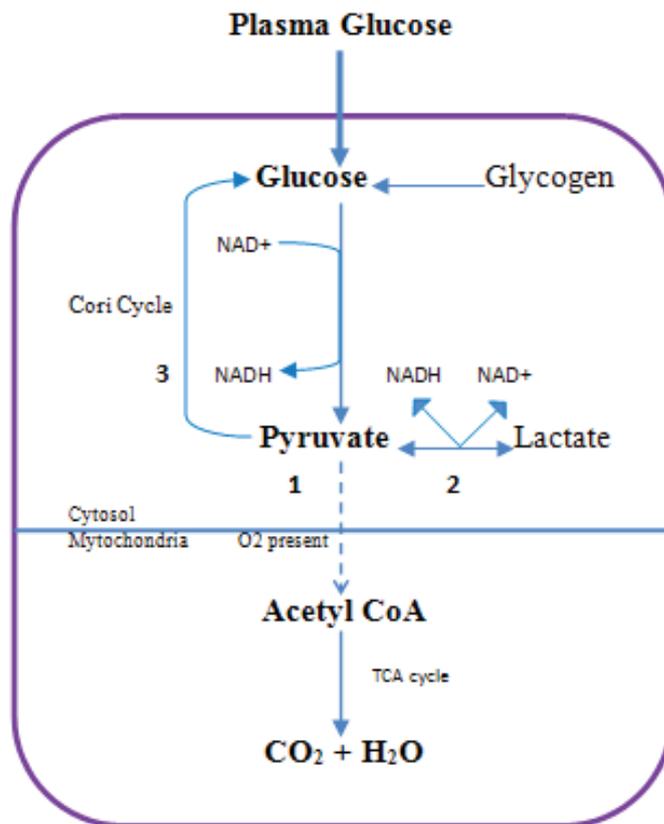
The patient was treated for DKA according to the Sisters of Charity UHC MICU standard protocol (intravenous bolus of insulin 0.1 mg/kg of body mass, followed by insulin in continuous infusion for 24 hours, 0.9% normal saline, potassium replacement, and 5% dextrose drip with insulin). Ketoacidosis improved, and the patient was discharged after full recovery on day 6. She was recommended to continue treatment with insulin.

### 3. Pathophysiology of lactic acidosis

Lactic acidosis is characterized by low blood pH (<7.35) and elevated arterial lactate (>5.0 mmol/L) [10]. The accumulation of lactate is usually due to enhanced pyruvate production, reduced pyruvate conversion to carbon dioxide and water, and altered redox state within the cell, Fig.1.

Simply put, lactic acidosis occurs when there is an imbalance between increased lactate production, impaired metabolism, and reduced clearance.

One of the mechanisms by which metformin increases plasma lactate levels is the promotion of glucose to lactate conversion in the splanchnic bed of the small



**Fig. 1.** Biochemistry of lactate production. Pyruvate, the only precursor to lactate, is produced in the cytoplasm from glucose metabolism via glycolysis (1). When oxygen is available, pyruvate enters the mitochondria and is oxidized to CO<sub>2</sub> and H<sub>2</sub>O in the tricarboxylic acid cycle (TCA cycle) (2). Under anaerobic conditions, pyruvate is unable to enter the mitochondria to be oxidized and is reduced to lactate (3). In the liver and kidney, pyruvate can also be converted to glucose. The Cori cycle describes a process by which lactate is produced by one tissue (muscle) and converted back to glucose in another tissue (liver). Lactate accumulates under anaerobic conditions. Adopted and modified from Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med* 2005; 20:255–271.

intestine and the inhibition of the mitochondrial respiratory chain complex 1, leading to the impairment of hepatic gluconeogenesis and inhibition of mitochondrial respiration in tissues responsible for lactate removal (i.e., liver, kidney, heart, skeletal muscle) [11,12].

Metformin is found as the cause of lactic acidosis when there is an increase in metformin plasma levels higher than 5 µg/mL [13]. Such an increase in plasma metformin concentrations (therapeutic range < 2 µg/

mL) [14] is observed in individuals with acute metformin overdose, poor renal function, impaired hepatic metabolism, severe dehydration, and in the presence of increased lactate production (i.e., sepsis, heart failure, reduced tissue perfusion, anoxia).

On the other hand, DKA is a result of absolute insulin deficiency, reduced glucose utilization, and enhanced lipolysis; increased delivery of free fatty acids (FFAs) to the liver coupled with raised glucagon levels promote FFA oxidation and the production of ketone bodies [15].

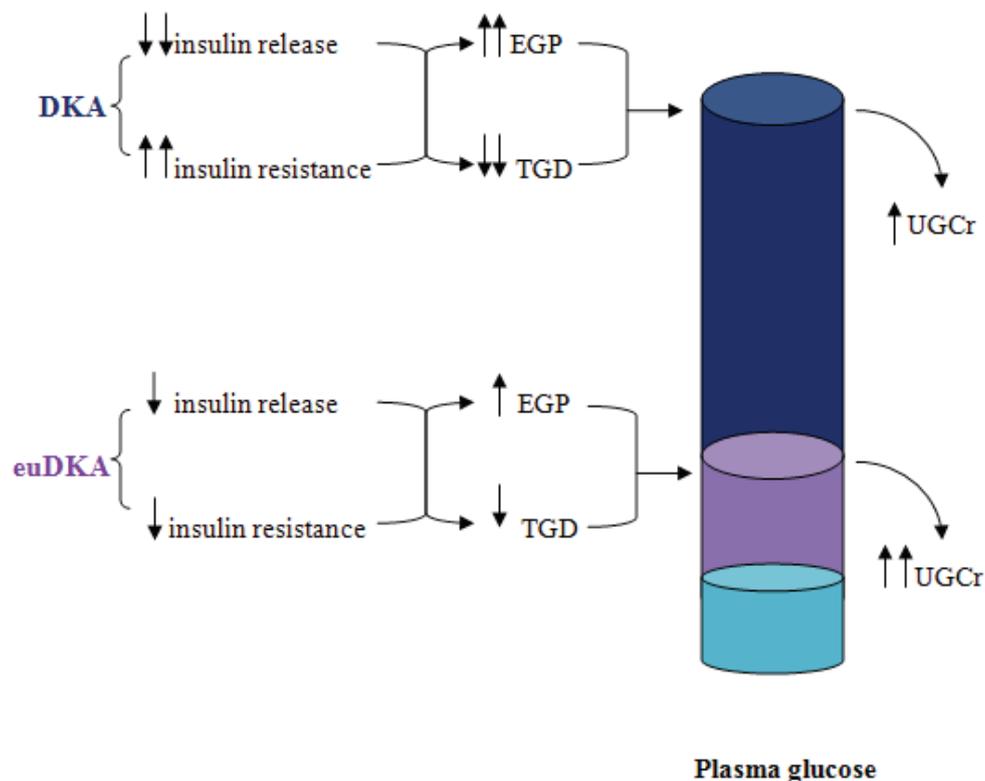
The most widely used diagnostic criteria for DKA include blood glucose over 13.8 mmol/L, arterial pH <7.3, serum bicarbonate <15 mEq/L, and a moderate degree of ketonemia and/or ketonuria [16].

Euglycemic diabetic ketoacidosis (euDKA) is reported in T2D patients with SGLT2 inhibitor treatment.

The difference in the pathophysiology of DKA- versus SGLT2 inhibitor-induced euDKA is schematized in Fig. 2.

In euDKA, insulin deficiency and insulin resistance are milder (insulin resistance may actually be improved); therefore, glucose overproduction and underutilization are quantitatively lesser than in DKA. More importantly, renal glucose clearance is twice as large with euDKA as with DKA [17,18].

Full-dose SGLT2 inhibition induces a rapid increase in urinary glucose excretion, ranging 50 - 100 g/day and lasting slightly longer than 24 hours. Thus it can make a significant fraction of daily carbohydrate availability [19, 20]. In previously performed study, patients who were treated with SGLT2 inhibitors [18], both fasting and postprandial plasma glucose levels decreased by 20 - 25 mg/dL (1.11 - 1.38 mmol/L). Taken into consideration that glucose is stimulus for insulin secretion, plasma



**Fig 2.** Essential pathophysiology of DKA and euDKA consequent to the use of SGLT2 inhibitors. TGD=tissue glucose disposal; UGCr=urinary glucose clearance rate. Adopted and modified from Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thevenet J et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med* 2015; 1:512-17.

insulin levels also decreased (fasting by 10 pmol/L in and postprandial 60 pmol/L).

In contrast, plasma glucagon concentrations increased significantly, partly because of a diminished paracrine inhibition by insulin [21], and possibly also because of decreased SGLT2-mediated glucose transport into  $\alpha$ -cells [22]. The calculated prehepatic insulin-to-glucagon molar concentration ratio dropped (from 9 to 7 mol/mol in the fasting state and from 29 to 24 mol/mol during a meal). Lower insulin-to-glucagon ratio stimulated lipolysis (circulating FFAs were 40% higher during the meal) and enhanced lipid oxidation (by 20% on average) at the expense of carbohydrate oxidation (which dropped by 60%). Nonoxidative glucose disposal (i.e., glycogen synthesis and lactate release) also decreased by 15%. The increased FFA delivery to the liver resulted in a mild stimulation of ketogenesis [18].

#### 4. Discussion

In the first case reported, no other etiology for severe lactic acidosis apart from metformin was found, despite metformin plasma concentration not having been measured since its determination was not available at that time.

The patient was a type 2 diabetic without risk factors for developing lactic acidosis such as acute renal failure. Also, there were no known precipitating factors that could have contributed to the severe lactic acidosis, such as signs of dehydration, the presence of toxic drugs, or an infection. The only factors recorded were the prescribed high doses of metformin and advanced age.

Published studies have reported a correlation between serum creatinine and plasma metformin, further they reported correlation between plasma metformin and arterial lactate [24].

Furthermore, the appearance of acute renal failure without previous renal dysfunction raises the issue of whether high doses of metformin in older patients could be responsible for acute renal failure with subsequent lactic acidosis due to drug accumulation, since metformin is excreted by the kidneys without being metabolized [24,25].

MALA is a rare, preventable, but life-threatening adverse event and should be strongly suspected in patients presenting with high anion gap metabolic acidosis and high blood lactate concentration. The daily metformin dosage should be no more than 2.5 g, and should be reassessed as the patient ages [24].

In the patient from the second case report, acute renal failure and dehydration after OSP ingestion and intravenous contrast application were the precipitating factors for MALA.

OSP and metformin are very common and widely prescribed agents for bowel preparation and T2DM control. Renal impairment after usage of OSP and lactic acidosis after metformin are both well recognized AEs [26,27]. However, the safety of OSP usage in patients taking metformin is seldom discussed.

The renal injury associated with OSP is termed acute phosphate nephropathy and is caused by the deposition of calcium-phosphate complex in the distal renal tubules [28].

Predisposing factors are old age, female gender, impaired renal function, diabetes mellitus, dehydration, hypertension, treatment with renin-angiotensin-aldosterone system inhibitors or diuretics, and hyperparathyroidism [29].

Therefore, we think that the co-ingestion of OSP and metformin along with intravenous contrast application is a dangerous combination which should be avoided in daily practice, even though metformin is not listed in the Agency of Medicinal Products and Medical Devices of Croatia (HALMED) notifications as a precipitating and contributory factor for possible adverse events in combination with OSP.

In the third patient, we described a severe ketoacidosis caused by a SGLT2 inhibitor, during dehydration and low-carbohydrate intake due to acute gastrointestinal viral infection. It has been recently shown that SGLT2 inhibitors increase endogenous glucose production, serum glucagon levels and serum ketone bodies [30-32]. During low carbohydrate intake, acceleration of urinary glucose excretion by SGLT2 inhibitors would

lead to severe glucose depletion and consequently to severe insulin deficiency. Insulin deficiency promotes ketogenesis, which can lead to ketoacidosis. In addition, dehydration in our patient has certainly contributed to the development of ketoacidosis. Consequently, strict low-carbohydrate diet and use of SGLT2 inhibitor potentially might cause ketoacidosis. Increased ketogenesis is caused by glucose depletion, which shifts energy metabolism towards increased utilization of fatty acids. The claim that starvation ketosis is not accompanied by acidosis is disputable [33].

We found one case report describing euDKA in a patient with Prader-Willi syndrome and T2DM, which was associated with the use of ipragliflozin, without additional precipitating factors. Thirteen days after the change in treatment, the patient developed DKA with a blood glucose level of 10.6 mmol/L and an undetectable urinary level of C-peptide. Prior to this event, the patient had followed a low-carbohydrate diet with an estimated carbohydrate intake of 66 g/day [34].

Another case report describes a 50-year-old woman with poor glycemic control, in whom canagliflozin 300 mg/day was added to a regimen of glipizide and metformin. This patient had reported current severe gastrointestinal symptoms and a 30-kilogram weight loss over 6 months, for which seemingly no action was taken. Ketonuria is not routinely assessed in most clinics. However, the typical symptoms this patient presented suggested that she may have had ketonemia or ketonuria, although not ketoacidosis, even prior to starting SGL2 inhibitor therapy. Starvation was suspected as the cause of ketosis in this case report [35].

In Japan, six SGLT2 inhibitors (ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin) are on the market. As of July 2015, a total of 28 cases of DKA or ketoacidosis have been reported. They also included two cases of DKA associated with carbohydrate restriction [36].

In addition, the U.S. Food and Drug Administration (FDA) recently made known that 20 cases of DKA, ketoacidosis, or ketosis associated with SGLT2 inhibitors had been reported from March 2013 (date of approval of the first drug in this class) through June 2014, and that in

some reports glucose levels were only mildly elevated at less than 11.1 mmol/L [7].

The FDA lists various precipitating factors which have been associated with reported episodes of acidosis or ketosis, such as acute illness, infection, reduced caloric/fluid intake, and reduced insulin dose [37].

In the event of any extra demand for glucose (e.g., pregnancy, starvation), a sudden cessation of glucose supply (e.g., low carbohydrate diet, fasting), or a lack of nutrient absorption (gastrointestinal upset), the SGLT2-inhibited body may not be able to maintain its homeostasis. After exhausting the hepatic and muscular glycogen reserves, the body will have to shift to gluconeogenesis and adopt a ketogenic metabolic pathway. The body shifts to gluconeogenesis and ketogenic metabolic pathway after exhausting glycogen reserves. A minimum of 100 g carbohydrates are required daily to prevent ketosis. Thus, SGLT2 inhibitors should be avoided in patients who are unable to consume this amount of carbohydrates [38].

Our patient's starvation was a result of acute viral gastrointestinal disease, vomiting, and diarrhea, which is why, in case of such an event, patients should be warned to change their T2DM therapy in agreement with their physician in order to avoid this adverse event.

## 5. Conclusion

The publication of cases of metabolic acidosis with SGLT2 inhibitor and metformin therapy highlights the need for increased awareness of both physicians and patients with T2DM. Patients with T2DM should be educated about the importance of regular fluid and food intake, whereas physicians should be more aware that the key to the effective use of all glucose-lowering medication is appropriate patient selection, counseling, and follow-up. There are no algorithms, guidelines, or investigations which can replace common sense. It is good clinical sense which will ensure that we are able to translate pharmaceutical advances into clinical benefits for people with T2DM who seek their physicians' advice.

## Acknowledgements

The authors wish to thank Aleksandra Žmegač Horvat, University of Zagreb School of Medicine, for language editing the text.

## Author contributions

MČ and VD conceived and designed the paper. JD, IP, IK, MT and VD collected and analyzed patients' data and search the literature. MČ drafted the manuscript, and VD contributed to its revision and final version. All coauthors contributed in discussion, draft changes, and approved final version of the paper. MČ and VD as a senior author take responsibility for the paper as a whole.

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