Sodium-glucose co-transporter-2 inhibitor-associated non-diabetic ketoacidosis: a case report

Vincenzo Trapanese,[1] Francesco Maruca,[2] Maria Resilde Natale,[1] Federica Giofrè,[1] Francesca Cosentino,[1] Silvia Sergi,[1] Giuseppe Armentaro,[2] Valentino Condoleo,[2] Franco Arturi[1,3]

[1]Internal Medicine Unit, Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro; [2]Geriatric Unit, Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro; [3]Research Centre for the Prevention and Treatment of Metabolic Diseases (CR METDIS), Magna Græcia University of Catanzaro, Italy

ABSTRACT

Ketoacidosis is considered an emergency metabolic disorder that can be triggered by starvation and alcohol consumption in addition to diabetes. We described an unusual case of ketoacidosis in a non-diabetic young man who presented to our hospital with a complaint of rapid and shallow breathing, weakness and nausea. Fourteen days back, due to heart failure, he started sodium-glucose co-transporter 2 inhibitors (SGLT2-i) in addition to fumarate bisoprolol, sacubitril/valsartan and eplerenone. Based on clinical examination, ketoacidosis was suspected, although his glucose and glycosylated hemoglobin levels were in range. Overall, based on the clinical and laboratory findings, the diagnosis of euglycemic non-diabetic ketoacidosis due to the use of the SGLT2-i was made and SGLT2-i has been discontinued. Although SGLT2-i are effective and safe drugs, it is advisable to carefully evaluate their use also in non-diabetic patients especially when hepatic fibrosis or incorrect eating habits are present.

Correspondence: Vincenzo Trapanese, University of Magna Græcia of Catanzaro, Viale Europa, Germaneto, Catanzaro, 88100, Italy.
Tel.: +39.09613647072.
Fax: +39.09613647192.
E-mail: vincenzo.trapanese@studenti.unicz.it

Key words: SGLT-2 inhibitor; ketoacidosis; ketogenic diet; Empaglifozin; non-diabetic.

Contributions: VT, FA, conceptualization, writing-review and editing; VT, methodology; VT, FM, FG, FC, MRN, SS, GA, AS, FA, writing-original draft preparation; FA, supervision. All the authors read and approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received: 12 March 2024.
Accepted: 15 March 2024.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2024; 18:1716
doi:10.4081/itjm.2024.1716

Introduction

The sodium-glucose co-transporter 2 inhibitors (SGLT2-i), also known as gliflozins, are one of the relatively new classes of oral antidiabetic drugs used primarily in type 2 diabetes mellitus (T2DM). Their action consists of inhibiting SGLT2 channels of the renal proximal convoluted tubule, which reabsorbs almost 90% of filtered glucose.[1] SGLT2-i decrease the renal threshold for glucose excretion from 180 mg/dL (10 mmol/L) to 40 mg/dL (2.2 mmol/L), with a higher glucose excretion in urine and consequently lower blood glucose levels. This effect induces a reduction of glucotoxicity and improvement in insulin sensitivity. Only four gliflozins are approved in Europe: dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin. SGLT2-i were first developed as oral hypoglycemic agents and they effectively guarantee a reduction of 0.6-0.9% in glycosylated hemoglobin (HbA1c) compared with placebo. Considering their pharmacodynamics, SGLT2-i hypoglycemic effect only compares in hyperglycemic conditions but it's important to underline that their action is independent of insulin sensitivity and β-cell reserve and hypoglycemic risk is reset. Moreover, SGLT2-i action depends on glomerular filtration rate (GFR); lower GFR reduces glycosuria.[2] Nevertheless, the inhibition of glucose reabsorption is pushed to the maximum at any level of GFR. In fact, HbA1c decreases to 0.79% in normal renal function, 0.3-0.4% in GFR range of 30-59 mL/min/1.73 m2, below 30 mL/min/1.73 m2 they are ineffective.[3] SGLT2-i also modify plasma insulin levels (which decrease) and plasma glucagon levels (which increase).[2] Because of their glycosuric effect (loss of calories), SGLT2-i also reduce weight.[4] All of these effects associated with a reduction in liver fat, tissue inflammation and increase of β-cell activity are the reason for delay in insulin requirement.[2] SGLT2-i, such as all drugs, obviously have some side effects. First of all, urinary tract infections due to

glycosuria: glucose in the urinary tract level facilitates bacteria proliferation. Therefore, it is necessary to educate patients to a better intimate hygiene in order to avoid also pyelonephritis or upper urinary tract infections.[2] We cannot forget euglycemic diabetic ketoacidosis (DKA) whose incidence varies from 0.16 to 0.76 events per 1000 patient-year. There are some risk factors such as malnutrition, infection, or vomiting. The etiopathogenesis is not completely known. Obviously, not all patients with SGLT2-i develop DKA. The evidence demonstrated that patients who were affected by DKA during SGLT2-i treatment were patients with type 1 diabetes mellitus or patients with T2DM and a β-cell insufficiency or patients with latent autoimmune diabetes in adults (LADA). LADA is an intermediate form between type 1 diabetes mellitus and T2DM and it is often misdiagnosed as T2DM. LADA is characterized by a slow progressive autoimmune destruction of pancreatic beta cells. This condition tends to manifest during adulthood, often around 35 years of age. So, physicians must use caution in patients with a long history of diabetes and a reduction of β-cell function and LADA.[5,6] Ketoacidosis (KA) is a metabolic disorder caused by the accumulation of ketoacids in the body. The most common type of KA is DKA.[7] There are other types of KA like starvation ketoacidosis (SKA) and alcoholic ketoacidosis.[7] Starvation usually triggers ketosis, but rarely leads to KA. SKA is associated with pregnancy, lactation, preoperative states and very low carbohydrate diets. In case of prolonged fasting and low carbohydrate intake, hepatocytes will generate another source of fuel for the body (ketone bodies). The key pathogenetic factor in the genesis of SKA is the imbalance between insulin and counter-regulatory hormones in the glycogen-private environment. In fact, low carbohydrate levels induce insulin reduction, causing lipolysis, which will lead to increased production of free fatty acids (FFA) from fat cells. The FFA will then be transported to the hepatocytes, whereby oxidation of the FFA, will produce acetyl-coa. Acetyl-coa stimulates a ketogenic pathway, which leads to ketone body production and acidosis. Metabolic acidosis is defined by the reduced level of pH and serum bicarbonate.[8] The physiological production of ketones increases during the first three days of fasting. SKA diagnosis is clinical. Metabolic disorders and clinical presentation in SKA are similar to DKA.[9] It's important to pay attention to the history of a period of acute or chronic starvation, increased metabolic needs (for example, pregnancy and lactation), presence of diabetes. The treatment principles are based on the administration of glucose to break the ketoacid production cycle.[10] This stimulates endogenous insulin production to restore the insulin-glucagon ratio to normalcy. It is also useful to make infusions of normal saline solution that replete extracellular liquid and chloride ions, thereby reducing counter regulators, and maintaining electrolyte balance.[11]

Case report

This case is about a 26-year-old non-diabetic male patient who presented to our hospital with a complaint of rapid and shallow breathing, malaise and nausea for a few hours. His past medical history included mildly reduced ejection fraction chronic heart failure (NYHA class II) secondary to already revascularized chronic post-ischemic dilated cardiomyopathy in patients with previous Kawasaki disease and moderate-grade hepatic steatosis with grade I hepatic fibrosis. Fourteen days back, for heart failure, he started Empagliflozin 10 mg orally once a day in addition to fumarate bisoprolol, sacubitril/valsartan and eplerenone. He also complained of dyspepsia and decreased oral intake. He fasted for around 12 hours. He denied alcohol consumption, illicit drug use, smoking or recent travel. On examination, he looked pale and distressed, not dehydrated nor jaundiced. He was conscious, on alert and oriented to time, place, and person. His height was 155 cm, body weight was 142 kg and body mass index was 59 Kg/m². Blood pressure was 120/80 mmHg, heart rate was 78 beats per minute, temperature was 36.5ºC, peripheral capillary oxygen saturation was 99% on room air, and respiratory rate was 22 beats per minute. Neurological examination showed normal tone, power, and reflexes. The rest of the head-to-toe examination was unremarkable. His fasting blood sugar level was 98 mg/dl, glycosylated hemoglobin levels were 5.6% and insulin level was 25 mU/L. The homeostasis model assessment – insulin resistance index was 6.05. Analysis of arterial blood gas and serum electrolytes revealed a high anion gap metabolic acidosis (HAGMA) characterized by a decrease in pH with hypocarbia, hypobicarbonatemia and an increase in anionic gap. Capillary ketones were 3,2 mmol/L. His urinalysis was significant for positive ketones and glucose. The rest of the blood investigations were all unremarkable. Overall, based on the clinical and laboratory findings (Table 1), the diagnosis of euglycemic non-DKA due to the use of the SGLT2-i was made. He was appropriately treated with a 10% dextrose infusion that gradually improved their metabolic profile leading to normalcy in <24 hours. Empaglifozin was not discontinued and was recommended with adequate hydration and avoiding prolonged periods of fasting by following a 6-meal diet. Unfortunately, one month after discharge, he had another episode of euglycemic non-DKA after fasting for around 12 hours. SGLT2-i-induced KA was confirmed and he was instructed to stop the medication. After Empaglifozin discontinuation, KA no longer occurred. Thus, six months later, for weight reduction, the patient began a very low-calorie ketogenic diet (VLCKD) without complications.

Discussion

SGLT2-i are a relatively new class of oral hypoglycemic agents due to the obvious cardiovascular and renal benefits. Therefore, they are now also used in the treatment of heart failure (HF) and kidney disease. In fact, SGLT2-i, with the inhibition of reabsorption of glucose and sodium, stimulate osmotic diuresis and natriuresis, with a consequent decrease of the cardiac preload, so a reduction of arterial blood pressure and afterload, and finally strengthening of subendocardial circulation. This effect is present both in diabetic and non-diabetic patients. A multitude of clinical trials demonstrates the efficacy of SGLT2-i in HF.[12] In the renal field, SGLT2-i reduce hyperfiltration decreasing glomerular capillary hypertension. This action reduces physical stress, oxygen requirement and albuminuria. This leads to better kidney oxygenation, with a consequent preservation of kidney function and GFR.[13] However, several studies have estimated that SGLT2-i increased the risk of KA in diabetic patients,[5] but these have not been documented in patients without diabetes.

Table 1. Results of laboratory investigations.

Investigations	Value	Reference range
pH	7.30	7.35-7.45
PCO2 (mmHg)	33	35-45
HCO3 (mmol/L)	19.1	24-28
Sodium (mEq/L)	141	136-145
Potassium (mEq/L)	4.4	3.5-5.1
Chloride (mEq/L)	103	98-107
Anion gap (mmol/L)	18.9	8-16
Lactate (mmol/L)	1.6	0.5-2.5
Capillary ketones (mmol/L)	3.2	<0.6
Urine ketone (mg/dL)	40	0
Urine glucose (mg/dL)	1000	0
Blood glucose (mg/dL)	98	74-106
HbA1c (%)	5.6	<6.5
Creatinine (mg/dL)	0.56	0.7-1.20
Urea (mg/dL)	35	10-50
AST (U/L)	18	<40
ALT (U/L)	26	<41

PCO2, partial pressure of carbon dioxide; HCO3, bicarbonate; HbA1c, glycosylated hemoglobin; AST, aspartate aminotransferases; ALT, alanine aminotransferase.

The case report discusses non-diabetic KA, a rare and life-threatening side effect of SGLT2-i. Metabolic acidosis is a common metabolic abnormality with a broad differential diagnosis, each with a different management plan and a different prognosis. This article presents a rare case of HAGMA with increased plasma and urinary ketones in a non-diabetic patient without alcoholic or toxicological exposure. HAGMA was associated with the use of SGLT2-i how heart failure treatment. HAGMA episodes had a short period (about 12 hours) of starvation before the presentation. This rare and unique form of HAGMA may be due to an altered physiological process. The plausible explanation for the triggering of HAGMA was multifactorial. The first trigger was the decreased serum glucose associated with the use of SGLT2-i. Indeed SGLT2-i inducing a major urinary glucose excretion, reduces glycemic levels and so insulin secretion from pancreatic β-cells. Insulin level reduction means a reduction of the antilipolytic activity of insulin so the body produces more FFA, converted to ketone bodies by β-oxidation in the liver. Moreover, SGLT2-i stimulates the secretion of glucagon, in addition to the stimulation induced by the decrease of insulin. Glucagon secretion also induces a boost in the production of ketone bodies.[5] The second trigger was the lack of glycogen reserves due to the presence of hepatic fibrosis as a result of the rearrangement of liver architecture.[14] The third trigger was starvation for about 12 hours together with the presence of insulin resistance.[7] Overall, the metabolism shifts from carbohydrates to lipids. Indeed, a decreased supply of glucose stimulates gluconeogenesis through increased counter-regulatory hormones (glucagon, cortisol, epinephrine and norepinephrine) and decreases glucose-dependent insulin release, leading to increased glucose levels and lipolysis, thus diminishing the supply of oxaloacetate and this hormonal imbalance triggering the process of ketogenesis. The cycle of ketogenesis was broken by providing glucose in the form of dextrose infusion.[10] The evidence that KA no longer occurred after the discontinuation of Empaglifozin or either during the VLCKD shows that SGLT2-i was the main cause of KA. This case shared striking similarities between clinical presentation and biochemical parameters with DKA. Non-DKA cases are usually euglycemic but they can rarely present with mild hyperglycemia.[15] Therefore, HbA1c and insulin level are a reasonable test to identify diabetes status. Inadequate administration of insulin can lead to dangerous hypoglycemia.[7]

Conclusions

Although the association of KA with SGLT2-i is not very frequent, given the potential adverse consequences, it is important to consider the reasonable suspicion in all patients, especially if it presents with nausea, vomiting, abdominal pain and severe dehydration. Blood gas analyses, plasma and urinary ketones would be performed on these patients, regardless of their blood glucose levels for early diagnosis and better prognostic outcomes. So, although Empaglifozin is an excellent drug, it's reasonable to use caution above all in patients with hepatic fibrosis due to limited glycogen reserve and with eating disorders. To increase safety, it may be helpful for patients taking SGLT2-i to avoid long periods of fasting and have frequent urine tests with a test strip for ketonuria.

References

1. Salvatore T, Carbonara O, Cozzolino D, et al. Kidney in diabetes: From organ damage target to therapeutic target. Curr Drug Metab 2011;12:658-66.
2. Salvatore T, Galiero R, Caturano A, et al. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. Int J Mol Sci 2022;23:3651.

3. Van Bommel EJ, Muskiet MH, Tonneijck L, et al. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to Clinical Outcome. Clin. J Am Soc Nephrol 2017;12:700-10.
4. Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation 2016;134:752-72.
5. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 2016;7: 135-8.
6. Kelley JL, Strum M, Riche DM, Chandler AM. Sodium Glucose Transporter 2 Inhibitors and Diabetic Ketoacidosis in Three Patients with Diabetes: Underlying Causation. J Pharmacol Pharmacother 2017;8:137-9.
7. Mahfooz RS, Khan MK, Al Hennawi H, Khedr A. SGLT-2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis: A Case Report and a Literature Review. Cureus 14:e26267.
8. Bashir B, Fahmy AA, Raza F, Banerjee M. Non-diabetic ketoacidosis: a case series and literature review. Postgrad Med J 2021;97:667-71.
9. Sloan G, Ali A, Webster J. A rare cause of metabolic acidosis: ketoacidosis in a non-diabetic lactating woman. Endocrinol Diabetes Metab Case Rep 2017;2017:17-0073.
10. Howard RD, Bokhari SRA. Alcoholic ketoacidosis (AKA). StatPearls 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430922/ (updated May 22nd, 2020)
11. Ghimire P, Dhamoon AS. Ketoacidosis. StatPearls 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534848/ (updated August 8th, 2023)
12. Lytvyn Y, Bjornstad P, Udell JA, et al. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation 2017;136:1643-58.
13. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu Rev Physiol 2021;83:503-28.
14. Owen OE, Reichle FA, Mozzoli MA, et al. Hepatic, Gut, and Renal Substrate Flux Rates in Patients with Hepatic Cirrhosis. J Clin Investig 1981;68:240-52.
15. Chandrasekara H, Fernando P, Danjuma M, et al. Ketoacidosis is not always due to diabetes. BMJ Case Rep 2014;2014:bcr2013203263.