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Case Report

Recognizing the Gap: A Case Series of Euglycemic and Hyperglycemic SGLT2 Inhibitor-Associated Diabetic Ketoacidosis

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ABSTRACT

Introduction: Ketoacidosis is a rare but serious side effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i), possibly overlooked in clinical practice. We aim to further characterize the presentation of and risk factors for SGLT2i-associated ketoacidosis to improve recognition in clinical practice.

Methods: Nine cases of diabetic patients identified with SGLT2i-associated ketoacidosis (DKA) at the University Hospital of Leipzig are presented in a case series.

Results: Euglycemia was detected in five out of nine cases. Symptoms varied, often remained unspecific and typical hallmark symptoms of ketoacidosis could not be identified in all cases. Four out of nine cases were female, and duration of diabetes disease and SGLT2i treatment, age and BMI showed a wide range. Risk factors most often identified were caloric restriction in six cases, infection in six cases, and insulin reduction in three cases. Urine ketone bodies were assessed and detectable in all cases, serum ketone bodies were only assessed in four cases but detected in each of these. Seven cases required ICU treatment, none were fatal.

Conclusion: SGLT2i-associated DKA may present in both, euglycemic and hyperglycemic form and with rather unspecific symptoms, all of which complicate recognition. Established risk factors were identified in all cases and their assessment can potentially facilitate recognition of SGLT2i-associated DKA. Presented cases underscore the importance to inform patients regarding risk behavior before initiating SGLT2i treatment to prevent ketoacidosis.

Keywords: Diabetic ketoacidosis; Sodium-glucose-cotransporter-2 inhibitors; Diabetes mellitus; Euglycemic; Hyperglycemic; Case report

Abbreviations: DKA-diabetic ketoacidosis; SGLT2-i - sodium-glucose cotransporter-2 inhibitors; UKL-university hospital of leipzig; d - day; ECG - electrocardiogram; GAD - glutamic acid decarboxylase anti bodies; IA-2-insulinoma-antigen-2 ; IAA-antibodies against insulin; ZnT8-zinc transporter 8; ICU-intensive care unit; IV intravenous; AKIN-acute kidney injury; BMI-body mass index; HCO_3-hydrogen carbonate; BE-base excess; LADA-latent auto-immune diabetes of adults

BACKGROUND

Sodium-glucose cotransport-2 inhibitors (SGLT2i/gliflozins) have been first approved in 2013 as a new class of glucose lowering medication used in the treatment of type 2 diabetes [1,2]. SGLT2i increase urinary glucose excretion which results in decreased blood glucose levels, caloric loss and weight reduction as well as mild osmotic diuresis with decreased systolic blood pressure, while maintaining a low risk of hypoglycemia [3-5].

Results from major clinical trials have further shown that SGLT2i improve patient outcomes in cardiovascular disease, chronic kidney

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disease, and reduce all-cause mortality and hospitalization rates for various reasons [6-10]. SGLT2i are now recommended by several medical societies, leading to an increase in prescription rates in patients with type 2 diabetes, heart failure, as well as chronic kidney disease [1-3].

Despite their undeniable beneficial effects, SGLT2i harbor the risk of Diabetic Ketoacidosis (DKA) as a rare but potentially life-threatening side effect for which warnings were first issued by the US Food and Drug Administration in 2015 followed by the European Medicines Agency in 2016 [11,12]. Recognition of SGLT2i-associated DKA can be challenging and may result in delayed appropriate therapy which is often argued to be the consequence of an atypical, euglycemic form of presentation [13-15]. However, there is growing evidence that SGLT2i-associated DKA presents with a wide range of glucose levels and may be accompanied by rather unspecific symptoms [13,16-18]. In addition, well-established risk factors associated with the development of SGLT2i-associated DKA could facilitate recognition but are often overlooked and not assessed systematically in clinical practice [13,14-19].

The aim of this work is to further characterize the profile of SGLT2i associated DKA and its potential risk factors to facilitate recognition in clinical practice and reduce delay of treatment.

INTRODUCTION

Identification of clinical cases

Patients admitted to the University Hospital of Leipzig (UKL) for diabetic ketoacidosis (DKA) between October 2020 and December 2023 were identified by screening all admissions for codes for DKA (E10, E11, E13, E14). Medical records of identified patients diagnosed with diabetic ketoacidosis were reviewed and included in this case series if they presented with ketoacidosis (pH<7.3; serum bicarbonate<18 mmol/l, elevated ketones) related to SGLT2i-intake. As previously defined, severity of ketoacidosis can vary from mild (arterial pH=7.25-7.30; serum bicarbonate [mEq/l] 15-18, anion gap>10; altered mental state) over moderate (arterial pH=7.00-7.24; serum bicarbonate [mEq/l] 10-15, anion gap>12; altered/drowsy mental state) to severe (arterial pH<7.00; serum bicarbonate [mEq/l]<10, anion gap>12; stupor/coma) [20]. Further, a cut-off value of 13.9 mmol/l was applied to differentiate euglycemic- from hyperglycemic ketoacidosis [14]. Only patients admitted and treated in the department of internal medicine were considered, surgical patients were not included in this analysis. Clinical data were obtained with the patient's informed written consent for scientific report publication. Relevant data extracted included patients' characteristics, clinical features, laboratory values and treatment courses. All procedures conducted were in accordance with the Helsinki Declaration in the current version (Fortaleza 2013) and approved by the Ethics Committee of the University Hospital of Leipzig.

CASE PRESENTATION

Ten cases were identified at UKL, but only nine consented in data analysis. Relevant characteristics of patients are summarized in Table 1. Their corresponding laboratory work up is presented in Table 2. The course of development of each case is described below to provide more detailed characterization of SGLT2i-associated DKA. Table 3, summarizes sample characteristics (Tables 1-3).

Table 1: Characteristics of patients identified with SGLT2i-associated DKA at UKL.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (years)	66	87	23	65	51	22	80	57	45
Sex	Male	Female	Female	Male	Female	Male	Male	Female	Male
Diabetes type	Type 2	Type 2	Type 3	Type 2	Type 2	Type 2	Type 2	Type 2	Type 2
Duration of diabetes	20 years	n.a.	9 years	9 years	4 month	8 days	15 years	10 years	7 years
BMI (kg/m^2)	25.8	24.6	24.8	20.8	22.3	32	28.6	31.2	31.4
SGLT2i (Dose)	Empagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg
Time to DKA post SGLT2i initiation	2 years	unknown	2 years	3 years	4 month	8 days	5 month	3 month	7 years
Risk factors	Alcohol abuse; UTI	UTI; Reduced caloric intake	Discontinued insulin; Pneumonia	Reduced caloric intake	Covid-Infection; UTI; Reduced caloric intake	Reduced caloric intake (dieting)	Decreased insulin	UTI; discontinued Insulin; Reduced caloric intake	UTI; Reduced caloric intake
Previous insulin use	Yes	No	Yes	No	No	No	Yes	Yes	No

Symptoms and signs of DKA	Kussmaul breathing; Dyspnea; Emesis; Polyuria; Confusion ; Abdominal pain; Fatigue Loss of appetite; Chest pain	Dyspnea; Polydipsia; Tachycardia	Somnolence; Tachypnoea; Fatigue; Tachycardia; Nausea; Emesis	Dyspnea; Kussmaul breathing; Tachycardia; Muscle pain	Abdominal pain; Fatigue; Nausea; Tachypnoea; Loss of appetite; Dehydration; Tachycardia	Fatigue; Dyspnea; Tachypnoea; Nausea; Emesis; Tachycardia; Hypotension; Dehydration; Polyuria; Polydipsia; Chest pain	Fatigue; Emesis; Dyspnea	Nausea; Emesis; Dizziness; Fatigue; Abdominal pain; Loss of appetite; Somnolence	Nausea; Emesis; Abdominal pain; Loss of appetite
ICU duration (days)	1	2	6	1	0	2	2	2	0
Duration hospital (days)	16	13	19	11	6	10	5	6	8
Fluid substitution	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Insulin substitution	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dextrose substitution	No	No	No	No	Yes	Yes	No	No	No
Anti-diabetic therapy when discharged	Insulin Metformin	Insulin	Insulin	Insulin	Metformin	Insulin	Insulin	Insulin	Metformin Sitagliptin Insulin

Abbreviations: BMI - body-mass-index; SGLT2i - Sodium-glucose cotransporter-2 inhibitor; ICU-intensive care unit; UTI - urinary tract infection

Table 2: Laboratory work up of patients identified with SGLT2i-associated DKA at UKL.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Presenting plasma glucose level (mmol/l)	6.9	24.0	23.0	13,2	9.2	7.30	30.0	22.1	13.3
pH	7.00	7.26	7.09	6.91	7.12	7.11	7.27	7.24	7.20
pCO^2 (mmHg)	28.9	13.8	23.6	19.7	15.8	19.7	34.6	38.4	31.5
HCO^3 (mmol/l)	14.8	6.0	6.90	3.7	5.1	6.0	15.4	16.0	12.0
Base Excess	-9.90	-20.3	-21.0	-26.3	-24.3	-21.8	-10.2	-9.9	-14.4
Anion gap (mmol/l)	20	26	24	22	16	20	22	20	12
Serum 3-hydroxybutyric acid (µmol/l)	>10000	n.a.	>10000	n.a.*	5035.0	808.3	n.a.	n.a.	n.a.
Serum ketones (µmol/ l)	>10000	n.a.	>10000	n.a.*	9473.0	1082	n.a.	n.a.	n.a.
Urine ketones (mmol/l)	(+) 2.8	(+) 7.4	(+) 7.4	(+) 7.4	(+) 7.4	(+) 7.4	(+) 8.0	(+) 7.4	(+) 7.4
HbA1c at admission (%)	7.0	9.4	7.5	8.9	8.4	11.4	13.9	11.7	10.8
Lactate (mmol/l)#	1.8	3.5	1.4	3.2	0.7	1.3	2.7	5.5	1.1

Note: Laboratory work up of patients identified with SGLT2i-associated DKA at UKL at admission prior to treatment initiation. Abbreviations: n.a. - not assessed; (+) - Ketone bodies in urine detected; *- Blood ketones were taken but data is missing due to pre-analytic sampling errors; #- Lactate was assessed in venous blood gas analysis.

Table 3: Characteristics of the population of patients identified with SGLT2i-associated DKA at UKL.

Patient´s characteristics	
Age (median/ IQR; years)	57.0 (65)
Sex (female |male; N [%])	4 [44.4%] | 5 [55.6%]
Diabetes duration (median/ IQR; years)	8,8 (23.6)
Diabetes Type (N[%])	Type 2: 8 [88.9%]| Type 3: 1 [11.1%]
BMI (median/IQR, kg/m^2)	25.8 (12.0)
Time to DKA post SGLT2i initiation (median/IQR; days)	437.5 (2547.0)
Previous Insulin use (yes|no; N [%])	4 [44.4] | 5 [55.6]
Symptoms and clinical signs	
Respiratory symptoms (N[%])	7 [77.8]
Hypotension (N[%])	1 [11.1]
Dehydration (N[%])	2 [22.2]
Polydipsia (N[%])	2 [22.2]
Polyuria (N[%])	2 [22.2]
Altered mental status (N[%])	3 [33.3]
Fatigue/Asthenia (N[%])	6 [66.7]
Abdominal pain (N[%])	4 [44.4]
Nausea (N[%])	5 [55.6]
Emesis (N[%])	6 [66.7]
Loss of appetite (N[%])	4 [44.4]
Tachycardia (N[%])	5 [55.6]
Chest pain (N[%])	2 [22.2]
Muscle pain (N[%])	1[11.1]
Risk factors	
Infection (N[%])	6 [66.7]
Reduced caloric intake(N[%])	6 [66.7] | unintentional 5 [55.6]
Decreased or discontinued insulin (N[%])	Decreased 1 [11.1] | discontinued 2 [22.2]
Alcohol consumption (N[%])	1 [11.1]
Diagnostic parameters	
Blood glucose at admission (median/IQR, mmol/l)	17.7 (23.1)
Euglycemic DKA (N[%])	5 [55.6]
Hyperglycemic DKA (N[%])	4 [44.4]
HbA1c (median/ IQR, %)	10.8 (8.6)
pH (median/ IQR)	7.12 (0.36)
pCO_2 (median/ IQR, mmHg)	23.6 (24.6)
Base Excess (median/ IQR)	-20.3 (16.4)
HCO_3 (median/ IQR, mmol/l)	6.9 (12.3)
Anion Gap (median/ IQR, mmol/l)	20.0 (10.1)

Serum 3-hydroxybutyric acid assessed (N [%])	4 [44.4]
Serum ketones assessed (N [%])	4 [44.4]
Urine ketones assessed (N[%])	9 [100%]
Treatment	
ICU treatment (N [%])	7 [77.8]
Duration of ICU treatment (mean /IQR, days)	1.0 (6.0)
Duration hospitalization (mean /IQR, days)	10.0 (14.0)
Dextrose substitution (N[%])	2 [22.2]

Note: Data are presented as median (interquartile range) or percent. Abbreviations: IQR - interquartile range; BMI - body mass index; ICU-intensive care Unit; DKA - diabetic ketoacidosis.

Case 1

A 66-year-old, overweight man with a 20-year history of type 2 diabetes was treated with insulin, metformin 2 g/day (d), and empagliflozin 10 mg/d which had been added to his daily medication two years ago. He presented with abdominal pain, loss of appetite, vomiting, dyspnea and Kussmaul breathing, confusion, and polyuria and reported fatigue during the past days. He further reported chest pain, but cardiac disease was ruled out immediately by electrocardiogram (ECG) and troponin reading. The patient had a history of regular alcohol consumption and alcohol abuse; however alcohol was not detected in his blood work at admission. Urinary tract infection, acute kidney injury (AKIN 2), and euglycemia were detected. Ketoacidosis required one day of intensive care unit (ICU) treatment with continuous IV insulin, fluid and potassium replacement. He was discharged after 16 days of treatment; anti-diabetic therapy was restarted with metformin and insulin, while empagliflozin was terminated.

Case 2

An 87-year-old, normal-weight woman was previously diagnosed with type 2 diabetes mellitus, and her antidiabetic therapy consisted of sitagliptin 50 mg/d, metformin 1 g/d and empagliflozin 10 mg/d, but the duration of SGLT2i-intake could not be ascertained. Due to pain in her knee joint she was unable to get out of her bathtub, where she had been confined for the past three days without food. She also was not able to take her medication while trapped in the bathtub. She had noticed an unusual thirst when drinking water from the tap and described increasing dyspnea and heart rate. On admission, she was diagnosed with a urinary tract infection, acute kidney injury (AKIN 3), and found to be in acidosis accompanied by hyperglycemic glucose levels. Autoantibodies against glutamic acid decarboxylase (GAD), insulinoma-antigen-2 (IA-2), insulin (IAA), zinc transporter 8 (ZnT8) were assesses as well as and c-peptide, which did not suggest misdiagnosed latent auto-immune diabetes of adults (LADA). Initially increased lactate rapidly decreased after fluid substitution while urinary ketones were elevated. Myocardial ischemia as an alternative trigger was ruled out *via* ECG and troponin reading. She required ICU treatment for two days with IV insulin, fluid, and potassium replacement. She was discharged after 13 days of hospitalisation with an insulin treatment regime.

Case 3

A 23-years-old, normal-weight female with cystic fibrosis had endocrine pancreatic insufficiency due to her underlying disease. Her diabetes mellitus type 3c had been treated with insulin for nine years and empagliflozin 10 mg/d was added to her treatment regimen two years ago. She presented with tachypnea and tachycardia, described fatigue during the past days and appeared increasingly somnolent. Prior to admission, she had also complained of nausea with recurrent emesis. Respiratory failure and decreased mental state due to severe ketoacidosis with hyperglycemia, aggravated by pneumonia required ICU treatment and invasive mechanical ventilation with continued IV insulin, fluid and potassium substitution for six days. She was discharged with an insulin treatment after 19 days of hospitalization, while SGLT2i treatment was terminated.

Case 4

A 65-year-old, normal-weight man was diagnosed with type 2 diabetes mellitus nine years ago and was treated with metformin 1 g twice daily and started on empagliflozin 10 mg/d three years ago. He had been hospitalized for further evaluation after being diagnosed with statin-induced immunologic myopathy two months earlier following weeks of severe muscle pain and weakness. Statin therapy was initiated one year earlier. During his hospitalization he skipped meals several times as he did not like the food. Five days after admission he reported increasing muscle pain and presented with increasing dyspnea, Kussmaul breathing, and tachycardia and severe ketoacidosis with near normal blood glucose was diagnosed. Initially elevated lactate rapidly cleared with fluid substitution while urine ketones persisted. Severe ketoacidosis resulted in ICU admission and one day of IV insulin, fluid, and potassium replacement. He was discharged after 11 days of hospitalization with an insulin treatment. SGLT2i treatment was discontinued.

Case 5

A 51-year-old, normal-weight woman had been diagnosed with type 2 diabetes four months earlier and was immediately started on empagliflozin 10 mg/d. She presented with increasing abdominal pain, nausea, and loss of appetite for the past two days, fatigue and clinical signs of dehydration, tachycardia, tachypnea and a positive COVID-19 test. She also reported an unintentional weight loss of 7 kg over the past 8 weeks which she attributed to work-related stress during which she had skipped meals recurrently given time constraints.

During hospitalization, the patient developed a urinary tract infection and complained of persistent symptoms. Ketoacidosis accompanied by euglycemia was diagnosed. Negative antibody diagnostic (GAD, IA-2, IAA, ZnT8) and normal c-peptide were not suggestive for misdiagnosed LADA. She was treated with IV

insulin, dextrose and fluids but was not admitted to the ICU. She was started on metformin, while SGLT2i treatment was terminated. She was discharged after six days of hospitalization.

Case 6

A 22-year-old man with obesity had been diagnosed with type 2 diabetes eight days earlier and was started on antidiabetic therapy the same day with metformin 500 mg in the evening and dapagliflozin 10 mg in the morning. On arrival he complained of nausea, emesis, chest pain, dyspnea and thirst, and described fatigue and polyuria. He was dehydrated, hypotonic and tachypneic. He reported that he had started a diet after being diagnosed with type 2 diabetes on the recommendation of his primary care physician. Thus, he had reduced his daily caloric intake by skipping meals and avoiding carbohydrates. As emesis increased, he felt unable to maintain food intake. Ketoacidosis and near-normal blood glucose levels were noted. Antibody diagnostic (GAD, IA-2, IAA) and normal c-peptide were not suggestive of type 1 diabetes. ECG and troponin reading ruled out cardiac disease. IV insulin, fluid and dextrose were initiated after ICU admission. He was discharged after 10 days of hospitalization with an insulin therapy regimen, without further SGLT2i treatment.

Case 7

An 80-year-old, overweight man, diagnosed with type 2 diabetes 15 years ago, has been using insulin on a basal-bolus regimen for the past 10 years and was started on empagliflozin 10 mg/d five months ago. He presented with increasing dyspnea, and emesis and reported fatigue over the past few days. Due to recurrent vomiting he continuously had been reducing his insulin dose, assuming that hypoglycemia was responsible for his decreased well-being. Mildly elevated lactate normalized after fluid substitution Ketoacidosis, severe hyperglycemia and acute kidney injury (AKIN 2) were detected and led to ICU admission, where he was treated with IV insulin, fluids, and potassium for two days. He was discharged after five days with further antidiabetic therapy consisting of insulin, only.

Case 8

A 57-year-old woman with obesity diagnosed with type 2 diabetes 10 years ago was treated with insulin alone until three months ago, when empagliflozin 10 mg/d was added. On admission, she reported fatigue and that she hadn't been able to eat for the past three days due to increasing nausea with emesis and abdominal pain and loss of appetite, which prompted her to stop using insulin. She increasingly experienced dizziness and became somnolent and blood work revealed hyperglycemia and acidosis, accompanied by urinary ketone bodies. Initially increased serum lactate rapidly decreased with continued fluid application. Antibody diagnostics (GDA, IA2, IAA) and c-peptide were not suggestive of a misdiagnosed LADA. Ketoacidosis resulted in ICU treatment for two days, where she received IV insulin, fluids and potassium. She was discharged after six days of hospitalization. SGLT2i treatment was terminated while an insulin treatment was reestablished and the patient was informed that reducing insulin most likely triggered SGLT2i-associated ketoacidosis fueling ketone body production.

Case 9

A 45-year-old man with obesity was diagnosed with type 2 diabetes seven years ago and had been treated with metformin 1 g/d and empagliflozin 10 mg/d ever since. He presented with nausea, emesis, dizziness, and described fatigue. He also complained about severe abdominal pain which had first started three days prior to admission and had led to reduced food intake. He reported weight loss of 7 kg during the past four months due to recurrent vomiting with reduced appetite and caloric intake. Laboratory blood work revealed a urinary tract infection and severe ketoacidosis accompanied by near-normal glucose levels. He was treated with IV insulin and fluids, but was not transferred to the ICU. He was discharged after eight days of hospitalization and was put on insulin, metformin and sitagliptin, while SGLT2i treatment was discontinued.

RESULTS AND DISCUSSION

The aim of this case series was to further characterize the presentation of and risk factors associated with SGLT2i-associated DKA to improve recognition of this potentially life-threatening condition in clinical practice and highlighting important pitfalls during SGLT2i treatment.

Characteristics, symptoms and clinical signs of SGLT2i-associated DKA

Of the nine cases of SGLT2i-associated DKA identified at UKL, only five can be classified as euglycemic ketoacidosis, applying the cut-off value of 13.9 mmol/l, as recommended [14]. This finding may facilitate recognition of SGLT2i-associated DKA in clinical practice as it underscores that SGLT2i-associated DKA can present with a wide range of blood glucose levels including hyperglycemia. This is consistent with a growing body of literature showing that SGLT2i-associated DKA does not necessarily present in a euglycemic fashion [16-18]. Further, our case reports highlight that symptoms often remain rather unspecific and typical hallmark symptoms expected in DKA, such as polydipsia, polyuria, dehydration, abdominal pain or change in mental status, may not always be present [13,14]. Thus, as summarized in Table 3, in patients of the present case series respiratory symptoms were most commonly detected which however, were rarely described as Kussmaul breathing. Further common symptoms were emesis, nausea, fatigue and tachycardia. The unspecific nature of symptoms may complicate the recognition of SGLT2i-associated DKA.

Interestingly, chest pain in the absence of cardiovascular disease was detected in two patients and similarly, muscle pain was mentioned by one patient, which had been classified solely as statin-induced. However, there is evidence that associates muscle pain with SGLT2i-use and both, muscle- and chest pain have been reported in other case reports of SGLT2i-associated DKA [21-23]. Nevertheless, the exact nature of these symptoms in the context of SGLT2i use needs further investigation.

As reported by others, patients with SGLT2i-associated DKA show a wider range of duration of disease as well as SGLT2i treatment, age and BMI, including normal weight and obese individuals [24]. This suggests that SGLT2i-associated DKA may not be limited to a specific demographic subpopulation, but may occur whenever SGLT2i are part of the treatment regimen.

Of note, one patient (case 2) developed SGLT2i-associated DKA despite not taking her medication for three days prior to diagnosis. This suggests a prolonged SGLT2i effect beyond the expected half-life of this drug which is estimated to be 12.9 hours for empagliflozin and dapagliflozin [25,26]. In this case renal damage may have contributed to an extended half-life and hyperglycemia

may have been the consequence of reduced renal glucose excretion with reduced diuresis, despite a lack of caloric intake [27]. Although exact mechanisms remain uncertain, this case is in line with previous reports of a prolonged SGLT2i effect which puts patients at risk to develop ketoacidosis even after treatment has been discontinued [18,27,28]. In this particular constellation a misdiagnosed LADA has to be considered as a differential diagnosis, which entails pancreatic beta cell dysfunction resulting in an absolute insulin deficiency and eventually hyperglycemic ketoacidosis. However, c-peptide and antibody diagnostics were not indicative of a misdiagnosed LADA in this case. Nevertheless, identifying patients misdiagnosed with type 2 diabetes while instead autoimmune beta cell destruction is evident is quite common in diabetic patients taking SGLT2i. Thus, one study reported a proportion of 22% who had a change in diagnosis of diabetes type as a result of DKA admission [18]. Change in diagnosed type of diabetes is seen in patients admitted with DKA under SGLT2i treatment, because misdiagnosed LADA comprise a predisposing condition for DKA development, as unrecognized absolute insulin deficiency fuels ketone production, eventually resulting in ketoacidosis [28]. Hyperglycemia nevertheless, may have been the consequence of absolute insulin deficiency in this case, resulting from beta cell failure during long-standing diabetes mellitus type 2.

Risk factors

Contrasting previous results, only four of the nine cases of SGLT2i-associated DKA identified at UKL were female. Usually it is reported that women are at greater risk to develop DKA when taking SGLT2i, although the exact reason for this association remains speculative [28]. One reason for diverging results might be the limited number of cases considered in this case series, which does not claim to be representative.

In each patient diagnosed with SGLT2i-associated DKA at UKL, known risk factors for this side effect were identified. These included infection, caloric restriction, insulin reduction and alcohol abuse [28,29]. Interestingly, reduced caloric intake in the course of intentional dieting for weight loss purposes was reported in one case, which had been recommended as part of the treatment of diabetes mellitus. Similarly, SGLT2i are often introduced to the therapy regime to decrease required insulin dosage. In these situations healthcare professionals face a therapeutic dilemma in which desirable approaches within the treatment regime of diabetes mellitus also comprise risk factors for SGLT2i-associated DKA. However, this dilemma can be resolved through properly educating patients regarding certain risk behaviors. Particularly caloric restriction and insulin reduction for any given reason but also alcohol consumption comprise preventable risk factors. Further, patients should be informed about an increased risk of ketoacidosis development during infectious diseases [30].

Beyond that, it is generally agreed on that insulin reduction, which per se is desirable once normoglycemia is achieved, should not exceed 20% of the initial insulin dosage to prevent SGLT2i-associated DKA [28]. Although these factors increase the risk of developing ketoacidosis they may also be used to facilitate recognition of SGLT2i-associated DKA through structured assessment in clinical practice. However, further research is needed to develop validated clinical risk scores.

Diagnostic and treatment

Urine ketone bodies were detected in all patients with SGLT2i-associated DKA. Serum ketone bodies were available in only four out of nine cases, but were found to be elevated whenever assessed. Often the assessment of both, urine and serum ketone levels are recommended to diagnose SGLT2i-associated DKA, probably as renal ketone body reabsorption might be increased by SGLT2i, and confounded urine diagnostics cannot be ruled out [14,31]. The present results suggest, that increased serum ketone levels are well reflected by the semiquantitative assessment of urinary ketone bodies, despite potential increased renal reabsorption. Taken together, our results indicate that SGLT2i-associated DKA can be diagnosed if, first, current or recent SGLT2i use is documented, second, metabolic acidosis is present (pH<7.3, serum bicarbonate<18 mEq/L), and third ketone bodies are detected in urine and/or serum, although the latter may only be necessary if urine diagnostic remains inconclusive, which may be rare. Fourth, the anion gap is elevated due to ketone body accumulation (>13 mmol/l). Blood glucose levels and clinical symptoms may be less informative as blood glucose levels can range from euglycemia to hyperglycemia and symptoms may be non-specific.

The majority, seven out of nine identified cases, required ICU treatment due to severe metabolic acidosis, but none were fatal. The management of SGLT2i-associated DKA is similar to that of classic DKA, although evidence-based management guidelines are lacking. After discontinuing SGLT2i intake, IV insulin substitution reduces further ketone body production, resulting in metabolic stabilization. Additional fluid and potassium substitution may be necessary. If SGLT2i-associated DKA presents euglycemic, dextrose substitution may be required to prevent hypoglycemia during insulin administration. In the presented cases dextrose application became necessary in only two out of five cases considered euglycemic.

CONCLUSION

The presented cases further characterize SGLT2i-associated DKA emphasizing an eu- and hyperglycemic form of presentation. Symptoms are unspecific and there may be a much broader spectrum than currently recognized. Clinicians should exclude DKA in any patient with reduced well-being while treated with SGLT2i. This should include the assessment of venous blood gases and urine and/or serum ketones. Point of care blood ketones should be available in any major hospital as ketone assessment in urine may be compromised due to renal ketone reabsorption. However, further evaluation of the additional value of serum ketone body assessment is needed. Type 1 diabetes and LADA should be excluded through antibody diagnostics (GAD, IA-2, IAA, ZnT8) and c-peptide assessment, if type of diabetes has not been confirmed prior or is questionable. Known risk factors have been identified in each case, so healthcare professionals should educate patients about risk behavior prior to SGLT2i treatment and structured assessment of risk factors may facilitate recognition of SGLT2i-associated DKA in clinical practice.

AUTHOR DISCLOSURE

TE has served as a paid consultant for Bayer, Lilly Deutschland, and Sanofi, and reports personal fees from Bayer, Boehringer Ingelheim, CME-Verlag, Fresenius Medical Care Deutschland, Lilly Deutschland, Novo Nordisk, Sanofi, and Dantis Pharmaceuticals. He has received research support from the European Foundation for the Study of Diabetes (EFSD Mentorship Programme, supported by AstraZeneca) and Otsuka Pharma. All other authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION

Imke Schamarek and Bastian Pasieka contributed equally to the manuscript. Imke Schamarek, Bastian Pasieka and Johannes Münch wrote the manuscript with input from all authors. Imke Schamarek and Bastian Pasieka collected clinical information. Bastian Pasieka, Thomas Ebert and Michael Stumvoll contributed to data collection and interpretation. All authors discussed the cases and contributed to the final manuscript.

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