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Diabetes Ketoacidosis Linked to Inhibitors of Sodium Glucose Co-Transporters in Diabetic Patients in Central America

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Abstract

Objective: To report the development of Diabetic Ketoacidos is (DKA) associated to Sodium-Glucose co-Transporter 2 (SGLT2) inhibitors in diabetic patients.

Materials and Methods: Clinical presentation, laboratory information and precipitating factors in diabetic patients with DKA associated with SGLT-2 inhibitors are described.

Results: In six patients with T1DM and one T2DM SGLT-2 inhibitors were added to help improve metabolic control and weight loss. Following a variable period of time with SGLT-2 inhibitors the patients presented nausea, vomiting, dehydration, moderate hyperglycemia, acidosis and ketosis. One patient had a urinary tract infection and all had marked reduction of total daily insulin replacement. DKA was of short duration and the patients did not present further complications. All the patients received IV insulin, volume replacement and required hospitalization.

Conclusion: Prescribing the lowest dose of SGLT-2 inhibitors and appropriately adjustment of total daily insulin administration can minimize the risk of DKA. In case the patient becomes sick the patient and the health care team must be vigilant and monitor capillary glucose and ketone bodies levels regularly.

Keywords: Diabetes ketoacidosis; Type 2 diabetes; Type 1 diabetes; SGLT2 inhibitors; Precipitating factors

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Abbreviations

BMI: Body Mass Index kg/m^2, DKA: Diabetes Ketoacidosis; HbA1c: Glycosylated Hemoglobin A1c; NPL: Lispro Protamine Insulin; SGLT 2: Sodium-Glucose co-transporter Inhibitors; GLP-1 rRA: Glucagon like Peptide Receptor Agonist

Introduction

Diabetes is a growing worldwide health problem which imposes an elevated risk for chronic complications and premature death [1-5]. Hyperglycemia, dyslipidemia, hypertension and inflammation are linked to the development of micro and macro vascular complications which can be prevented with optimal glycemic control and management of other risk factors [4-9]. Indeed, recent reports have shown that diabetic persons without risk factors have similar mortality as those without diabetes [10].

Management of hyperglycemia must consider patients age, presence of cardiovascular and renal complications and avoidance of adverse effects such as hypoglycemia [11-13]. Hypoglycemia is an iatrogenic complication associated with increased risk of death and represents a barrier to achieving glucose control [14,15]. Thus, efforts must be exercised to prevent this complication.

Hyperglycemia control, although a complicated task, has been facilitated with the introduction

Table 1: Pertinent Clinical Characteristic and Treatment Regimens of Type 1 Diabetic Patients with DKA.

Case	1	2	3	4	5	6	7
Age	22	27	22	36	38	24	35
Sex	Fem	Fem	Fem	Fem	Fem	Fem	Masc
Diabetes Duration (years)	14	4	5	20	27	2	0
BMI (kg/m2)	22.1	29.8	22.3	25.5	23.1	21.6	37.0
Blood pressure (mmHg)	104/70	104/64	130/90	110/80	125/70	106/64	160/100
Heart rate (bpm)	90	116	120	120	110	116	96
Respiratory frequency	16/min	18/min	32/min	18/min	19/min	16/min	16/min
Prior DKA	No	No	No	No	No	No	No
Prior treatment	Insulin infusion pump. Total daily insulin: 40 U	Basal-bolus Total daily insulin: 64 U	Basal-bolus Total daily insulin: 40 U	NPH BID + prandial regular insulin. Total daily insulin: 62 U	Basal-bolus Total daily insulin 72 U	Insulin infusion pump. Total daily insulin: 45.7 U	Basal insulin dose is total: 10 U, Dulaglutide 1.5 semanal, Metformina 1000 mg/Empagliflozina 25 mg
Current Treatment	Insulin pump 40 U/day + Canagliflozin 100 mg	Basal-bolus Total daily insulin: 64 U + Dapagliflozin 10 mg	Basal-bolus Total daily insulin: 64 U plus Canagliflozin 100 mg	Lispro+NPL. Total daily insulin 45 U + dapagliflozin 10 mg	Basal-bolus Total daily dose 72 U Dapagliflozin 10 mg	Insulin pump 40 U/ day + Empagliflozin 10 mg	Metformin 2000, Empaglifozin 25, daily and Dulaglutide 1.5 weekly
Duration of SGLT-2	8 months	24 months	2 months	25 months	13 months	8 months	72 hours
Precipitating factors	Insulin pump failure with reduction in insulin delivery	Diarrhea, hyporexia, Insulin suspension	50% reduction of insulin administration Vomiting, diarrhea	Insulin suspension	Fasting and dehydration possible urinary UTI	Insulin pump failure with reduction in insulin delivery	Diarrhea, Vomiting, dehydration

ITU: Urinary Tract Infection; CAD: Diabetic Ketoacidosis; SGLT-2: Sodium Glucose Co-Transporter, Basal bolus regiment with insulin analogues

of a number of efficacious new anti-hyperglycemic agents [16-19]. For example, SGLT-2 inhibitors indicated for the treatment of T2DM patients alone, as an adjective therapy with other oral agents or with insulin to improve glucose control with few side effects [16-19]. Also, these agents have demonstrated cardiovascular and renal benefits in T2DM patients and low rates of hypoglycemia [20-24].

However, SGLT-2 inhibitors are associated with a potential life-threatening complication such as DKA [25-28]. DKA seems to appear more commonly in patients undergoing surgery, inter current illness, and significant reductions in insulin provision [25-28].

A number of clinical trials published showed improved glycemic control, prevention of hypoglycemia and weight reduction. Despite the benefits of SGLT-2 inhibitors as an add-on therapy to insulin in T1DM the US Food and Drug Administration (FDA) advisory committee has not approved SGLT-2 inhibitors, as an adjunct therapy to insulin in adults with T1DM [29-34]. In contrast, EMA favored the indication of dapagliflozin and sotagliflozin for adults with T1DM [35].

In Central America SGLT-2 inhibitors are popular and widely used in T2DM and also in T1DM patients. In this report we describe seven diabetic patients from this region who developed DKA linked to SGT-2 inhibitors.

Case Presentation

Case 1

A 22-year-old female T1DM patient treated with an insulin infusion pump (Medtronic 640 g, total daily insulin dose of 40 U) and canagliflozin 100 mg was admitted into the hospital in DKA. Six days before hospitalization the patient presented recurrent hyperglycemic episodes. The day of admission, the patient had nausea, vomiting, headache and malfunctioning of the infusion set was detected.

Case 2

A 27-years old female T1DM patient developed DKA. The patient has been treated with basal bolus regimen (total daily insulin dose of 64 U) and dapagliflozin 10 mg. Ten days before admission the patient had fever, abdominal pain and diarrhea. She was anorexic and discontinued prandial insulin doses while maintained 34 U of basal insulin and dapagliflozin 10 mg. Three days later basal insulin was further reduced to 20 U and one day before admission the patient stopped completely insulin treatment but maintained dapagliflozin 10 mg.

Case 3

A 22-year old female with T1DM treated with basal bolus regimen (total daily insulin dose of 40 U) and canagliflozin. Two months after initiation of canagliflozin the patient discontinued prandial insulin. Three days before admission the patient also reduced basal insulin by 50% and presented fever, chills, perspiration, vomiting and diarrhea and was hospitalized in DKA.

Case 4

A 36-year-old female with T1DM was treated with lispro/NPL (0.68 U/Kg) and dapagliflozin 10 mg. She was hospitalized unconscious due to a head trauma. While being unconscious in the Emergency Department she did not receive insulin, or dapagliflozin. After 24 h since the accident, the patient presented a profound breathing pattern and the laboratory tests were consistent with DKA.

Case 5

A 38-year-old female with T1DM treated with a basal-bolus regimen (total daily insulin dose of 72 U) and dapagliflozin 10 mg once daily was admitted with DKA. The patient had severe emotional stress with panic attacks and was treated with anxiolytic and antidepressant medication. Three days before admission the patient had a urinary tract infection which was treated with oral antibiotics. The patient

Table 2: Pertinent laboratory results in diabetic patients with diabetic ketoacidosis.

Case	1	2	3	4	5	6	7
Glycaemia (mg/dL)	190	372	186	283	295	256	174
HbA1c (%)	7.4	7.6	8.7	7.2	7.3	7.5	12.45
pH	7.21	6.81	6.9	6.88	7.15	7.09	7
pCO2 (mmHg)	22.4	22.6	5.6	11	12.1	22.4	11
Bicarbonate (mmol/L)	13	3.5	4.6	2	4.1	8.3	3.6
Ketonuria (mg/dL)	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Ketone bodies	Positive	Positive	Positive	ND	Positive	NA	NA
Blood urea nitrogen (mg/dL)	27.0	16.1	15.2	22.1	20.5	18.0	9.4
Creatinine (mg/dL)	0.94	1.05	0.75	1.2	1.15	1.5	0.8
Na (meq/L)	135	130.6	132	141	132	141.9	138
K (mEq/L)	3.99	3.82	4.63	5.78	4.0	4.59	3.9
Chlorurom (mEq/L)	102	111.6	108	119	110	109	103
Osmolality (mosm/Kg	290.2	289.9	279.7	292	301	370	295
Anion gap (mEq/L)	20.3	15.5	19.4	20	21.8	24.6	14.7

Bicarbonate18.5-25.4, Osmolality 275-295, Anion gap 3-11, NA: Not available

presented nausea, vomiting, did not eat properly and reduced insulin administration.

Case 6

A 24-year-old female patient with T1DM treated with an insulin infusion pump (Medtronic 640 g, total daily insulin dose of 47 U) and 10 mg of empagliflozin. The patient developed nausea, abdominal pain, anorexia and was admitted into the hospital with DKA eight hours after the initial symptoms. An obstruction of the catheter of the infusion pump was documented.

Case 7

A 35-year-old obese male newly diagnosed with T2DM was treated with 1.5 mg dulaglutide once weekly, 10 U glargine insulin U-300 daily and12.5/1000 mg empaglifozin/metformin twice daily. Three weeks later, insulin was withdrawal; few h later presented with diarrhea, nausea, fatigue and was admitted into the hospital with DKA.

In all the patients the SGLT-2 inhibitors were added to improve glucose control and induce weight loss. As shown in Table 1, the SGLT-2 inhibitors were introduced several months before DKA in T1DM patients. In all the patients the dose of the SGLT-2 inhibitor was the same as that indicated for T2DM patients. In the newly diagnosed T2DM patient, theSGLT-2 inhibitor was initiated in combination with other anti-hyperglycemic agents three weeks before DKA. None of the patients had chronic diabetic complications.

On admission the patients were evaluated in the Emergency Department or in the Intensive Care Unit of tertiary facilities of Costa Rica, El Salvador and Guatemala. Arterial blood gases, hematocrit, white blood cell count, electrolytes, renal and liver function tests, urine smear and urine culture, electrocardiogram, thorax X-rays and abdominal ultrasound were done as appropriate. In all cases the SGLT-2 inhibitor was discontinued on admission. DKA was treated as per protocol and were discharged 2 to 4 days after. Table 1 summarizes other pertinent clinical characteristics of the study patients and Table 2 listed laboratory results of the patients with DKA [36].

Discussion

In this report, we describe six T1DM and one T2DM who developed DKA. The T1DM patients were treated with SGLT-2 inhibitors as an adjunctive therapy due to persistent hyperglycemia, overweight and obesity. Four of the T1DM patients were on a basal bolus regimen and two on insulin infusion pump. In the newly T2DM patient, the SGLT-2 inhibitor was part of the combined initial anti-hyperglycemic therapy including 10 U of basal insulin.

In T2DM, SGLT2 inhibitors reduce fasting, postprandial glucose, and HbA1c levels with low rates of hypoglycemia [16-19]. In conjunction with its glucose lowering effects, SGLT-2 inhibitors promote weight loss, have beneficial effects on blood pressure, uric acid concentrations, cardiovascular mortality and preserve renal function patients with T2DM [20-24]. As expected, these agents are widely used in high risk T2DM patients, but a number of reports have also shown improvement in glycemic control T1DM patients [25-34].

Relatively common side effects of SGLT-2 inhibitors are genital mycotic and less frequently urinary tract infections, both of which respond to usual therapy of particular concern is the association of SGLT-2 inhibitors with DKA [25-28,30].

In Europe, two of the SGLT-2 inhibitors were recently approved for its use in T1DM patients with special considerations [35]. This treatment should be contemplated in overweight or obese T1DM patients and exercising proper of diabetes education about predisposing risk factor for DKA and how to distinguish the clinical manifestations of DKA [35]. In addition, insulin dose should be appropriately reduced to avoid hypoglycemia and by using the lowest dose of SGLT-2 inhibitor, DKA risk would be minimize.

As indicated in Table 1, DKA occurred in our T1DM patients receiving SGLT-2 inhibitors along with reductions in insulin provision. Insulin administration was markedly reduced or discontinued due to pump failure in two cases. Likewise, in the other patients treated with a basal-bolus regimen, 50% reduction or even discontinuation of insulin administration followed, when the patients presented anorexia, vomiting, diarrhea or when the patient was unconscious due to a head trauma. In the newly T2DM patient with insulin resistance and impaired insulin secretion due to glucotoxicity, it was clear that the initial insulin dose was low and it was prematurely discontinued, while SGLT-2 was maintained.

In our case series additional contributing factors for the development of DKA were prolonged fasting, dehydration and urinary tract infections which precipitated DKA [25-32]. Of notice, in all our T1DM patients the doses of SGLT-2 inhibitor was that indicated for T2DM. Different doses of the SGLT-2 inhibitor were tested to evaluate the appropriate dose of SGLT-2 inhibitors in T1DM [33-34]. In the DEPICT study, DKA occurred in four and five participants on 5 mg and 10 mg dapagliflozin, respectively and, in three participants on placebo [32]. Furthermore, the EASE-3 trial showed that with a lower dose of 2.5 of empagliflozin, there were three cases of DKA in the placebo and empagliflozin group, respectively [33]. Similar results were obtained with sotagliflozin [34].

The pathophysiology of SGLT-2 inhibitor linked to DKA involves an imbalance between insulin and the counter-regulatory hormones including glucagon, cortisol and catecholamine [39-45]. Alterations in insulin/glucagon ratio can lead to exaggerated lipolysis from adipose tissue and increased ketogenesis [39-45]. Due to the glycosuria effect of SGLT-2 inhibitors, the patients with DKA linked to these classes of antihyperglycemic agents had moderate hyperglycemia [25-28]. Of note, two of our T1DM patients had moderate hyperglycemias, consistent with euglycemic DKA [25-27].

DKA associated with SGLT-2 inhibitors is uncommon. A meta-analysis of randomized controlled clinical trials reported meaningless effect of the medications on the presence of DKA [42]. After the alert made by the FDA, the incidence of SGLT2 inhibitors associated DKA was less than 1/1000 in controlled trials and 1.6/1000 person-years in cohort studies [42]. Noteworthy, due to the increasing number of patients receiving SGLT-2 inhibitors worldwide, including Central America, it may be possible that more cases of SGLT2 inhibitors associated DKA would be reported in the future. In controlled clinical trials the rigorous exclusion criteria of participants reassure that patients at risk for DKA are not included. Meanwhile, in the usual clinical setting the use of SGLT2 inhibitors may be more flexible, diabetes education is not commonly guaranteed and the strict monitoring of the patients could be less strict. Indeed, we have previously published the case of two patients who developed DKA associated with the use of SGLT-2 inhibitors in the setting of a several precipitating factors in Central America [37-38].

At discharge our patients received a basal-bolus regimen and the insulin infusion pump was re-installed in case 1 and 6. Except for case 3 and 5, the rest continued with SGLT-2 inhibitor at lower doses as an add-on therapy, by indication of the physician in charge of each case. At least six months after the DKA the patients had not reported recurrent DKA episodes.

Patients and physicians must be aware of the risk of DKA if insulin provision is reduced particularly in T1DM when SGLT-2 inhibitors are added as previously reported [37]. Also, alert must be paid in T2DM patients with relative insulin deficiency and prone to develop DKA in the presence of stressful conditions [38].

Furthermore, it is recommended that patients must report any suspicious manifestation of DKA and to monitor ketone levels if they become sick in order to mitigate DKA risk [46-47].

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