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Original article

Clinical characteristics of diabetic ketoacidosis in users and non-users of SGLT2 inhibitors

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ABSTRACT

Aim. – This study investigated the clinical characteristics of diabetic ketoacidosis (DKA) and compared the DKA characteristics between patients treated with and without SGLT2 inhibitors.
Methods. – Data were collected from patients aged ≥ 18 years admitted for DKA at nine centres in Korea between September 2014 and April 2017. The electronic medical records of these subjects were retrospectively reviewed. Based on their history of medications taken before admission, subjects were classified as either users or non-users of SGLT2 inhibitors and their clinical characteristics of DKA were compared.
Results. – During the study, the main subtype of DKA episodes (n = 523) was identified as type 2 diabetes (51%). Average hospitalization duration was 11 days, and average intensive care unit (ICU) time was 2.5 days. The in-hospital mortality rate was 3%, but no users of SGLT2 inhibitors died during DKA treatment. In patients taking SGLT2 inhibitors (n = 15), DKA manifested at 124 days, on average, after starting the inhibitors (range: 7–380 days). Also, SGLT2 inhibitors users had significantly lower plasma glucose levels (413 mg/dL) compared with non-users (554 mg/dL), and longer ICU stays (4 vs. 2 days; P = 0.019).
Conclusion. – In this report of recent data on the clinical features of DKA in Korea, patients using SGLT2 inhibitors needed longer treatment in ICUs compared with non-users and had lower levels of blood glucose, whereas DKA associated with SGLT2 inhibitors was rare.
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Introduction

Diabetic ketoacidosis (DKA) is the most serious acute complication of diabetes and requires hospitalization for prompt management. DKA is strongly associated with type 1 diabetes (T1D), but may also develop in those with type 2 diabetes (T2D) who experience a critical illness or have the atypical 'ketosis-prone diabetes'. The incidence of DKA has increased worldwide along with the prevalence of diabetes, but may also show a static trend [1,2]. In Korea, reported episodes of DKA have increased over the last two decades [3] despite more accessible healthcare services and improved socioeconomic status. Furthermore, the incidence of T2D has drastically increased compared with T1D in this country. As such, the clinical characteristics and outcomes of DKA may be changing over time.

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Sodium–glucose cotransporter-2 (SGLT2) inhibitors have been widely used in the treatment of T2D since their US Food and Drug Administration (FDA) approval in 2013. However, since then, reports have appeared through the Adverse Event Reporting System (AERS) of DKA in patients with diabetes treated with these inhibitors [4,5]. These agents lower plasma glucose levels by promoting renal excretion of glucose [6], which reduces the insulin-to-glucagon ratio and enhances lipolysis, thereby stimulating the production of ketone bodies in the liver [7]. Thus, SGLT2 inhibitors are associated with an increase in serum ketone levels. In the present multicentre study, recently reported clinical characteristics of DKA were compared between SGLT2 inhibitor users and non-users in South Korea.

Methods

Ethics statement

The study protocol, which conforms with the ethics guidelines of the Declaration of Helsinki, was approved by the institutional review boards of each participating hospital.

Research design

The study used data from nine hospitals, including four tertiary-care centres, in South Korea, and identified patients aged $\geq$ 18 years with DKA admitted to any of those hospitals between September 2014 and April 2017. (Note that dapagliflozin, ipragliflozin and empagliflozin were approved in September 2014, August 2015 and May 2016, respectively, in South Korea.) From among patients admitted with International Classification of Disease 10th revision (ICD-10) codes for DKA (E10, E11, E13, E14), our study selected subjects who showed the presence of both metabolic acidosis (serum bicarbonate $<$ 18 mEq/L, anion gap $>$ 10 and/or arterial pH $<$ 7.3) and ketones in either urine or blood. Also, their electronic medical records were retrospectively reviewed and the relevant data extracted, including a history of any antihyperglycaemic agents taken before admission, potential risk factors for DKA, patient characteristics, clinical manifestations, laboratory results, and treatment course and outcome.

Subtypes of diabetes were classified into five categories:

- T1D;
- latent autoimmune diabetes in adults (LADA);
- T2D;
- other specific types of diabetes;
- unknown.

This classification was performed by reviewing electronic medical records for duration of diabetes, requirement for insulin therapy, presence of antibodies against glutamic acid decarboxylase (GAD) and levels of C-peptide associated with DKA. Other specific types of diabetes, such as those associated with diseases of the exocrine pancreas and endocrinopathies, and drug-induced diabetes, were defined according to American Diabetes Association (ADA) classification guidelines. Patients not diagnosed with a specific diabetes subtype because they had not been examined for such a determination at the time of DKA events and those not followed-up after DKA events were classified as 'unknown'.

Serum C-peptide levels were measured by radioimmunoassay (RIA/IRMA; IMMUNOTECH, Prague, Czech Republic, at Ajou University Hospital, Inha University Hospital, Korea University Hospital and Soonchunhyang University Hospital), by chemiluminescence immunoassay (CLIA; Roche Diagnostics, Risch-Rotkreuz, Switzerland, at CHA Medical Centre, Gwangmyeong Sungae Hospital, National Health Insurance Service Ilsan Hospital and Ilsan Baik Hospital) or by chemiluminescent microparticle immunoassay (CMIA; Abbott Laboratories, Abbott Park, IL, USA, at St. Vincent's Hospital). In cases of DKA associated with SGLT2 inhibitors ('users'), further detailed information, including the specific generic name of the SGLT2 inhibitor, medication period and background medication, was also collected. Patients lacking data on their previous history of antihyperglycaemic agent use (n = 48) were excluded from our analyses.

Statistical analyses

Continuous variables are presented as means $\pm$ standard deviation (SD) or medians (interquartile range; IQR). Based on assessment of the normality assumption using the Kolmogorov–Smirnov test, either Student's t or Mann–Whitney U tests were used to compare continuous variables. The chi-squared (χ^2) or Fisher's exact tests were used to compare characteristics between users and non-users; these categorical variables are presented as numbers and percentages. A two-sided P-value $<$ 0.05 has been used to reflect statistical significance. All data were analyzed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA).

Results

Characteristics of patients with DKA

The mean age of our subjects (n = 523) was 46.5 $\pm$ 17.6 years, and their average diabetes duration was 7.7 $\pm$ 8.4 years (Table 1). Patients with T2D accounted for more than half (n = 266) of all DKA episodes, whereas 42% (n = 218) of episodes involved patients with either T1D or LADA. When DKA severity was determined based on arterial pH, 35% of patients exhibited mild DKA (pH $\geq$ 7.25), 51% had moderate DKA (pH 7.00–7.24) and 13% had severe DKA (pH $<$ 7.00). Overall, 26% of subjects had not been treated with antihyperglycaemic agents, and 22% were newly diagnosed with diabetes. Precipitating factors for DKA were identified in 93% of patients: the main contributing factor was non-compliance with care. On average, patients were admitted to an intensive care unit (ICU) for 2.5 days and received hospital care for 11 days. The in-hospital mortality rate was only 3% for all subjects; however, none of these deaths involved users of SGLT2 inhibitors.

DKA features in users vs. non-users of SGLT2 inhibitors

On average, DKA episodes developed after 124 days (range: 7–380 days) of starting SGLT2 inhibitors (Table 2). More users of these agents (73%, n = 15) had T2D than non-users (50%, n = 508; Table 1). Four cases of DKA in users (26%) were diagnosed as either T1D (n = 2) or LADA (n = 2) after a DKA event (Table 2). A greater proportion (87%) of users were also given oral hypoglycaemic agents without insulin than were non-users (14%), most likely because SGLT2 inhibitor users were being treated for T2D at the time. Indeed, subjects using SGLT2 inhibitors had significantly lower levels of glucose (413 mg/dL) at the time of their initial visit than did non-users (554 mg/dL; P = 0.006). Users also had significantly longer ICU stays (4 days) compared with non-users (2 days; P = 0.019), although their overall hospital stays were not longer (9 days) than non-users' (8 days; P = 0.372).

Discussion

The present study has examined the clinical characteristics of a large number of DKA episodes, and compared them between users and non-users of SGLT2 inhibitors. Previous reports have presented

Table 1
Baseline characteristics and diabetic ketoacidosis (DKA) features in users and non-users of sodium–glucose cotransporter-2 (SGLT2) inhibitors.

		Total	Users	Non-users	P[a]
Subjects (n)		523	15	508	
Male		299 (57)	7 (47)	292 (58)	0.436
Age (years)		46.5 ± 17.6	46.0 (36–63)	46.4 (32–58)	0.399
Duration of diabetes (years)		7.7 ± 8.4	4 (2–19)	5 (0–11)	0.529
Diabetes subtype:					
		189 (36)	2 (13)	187 (37)	0.159
	LADA	29 (6)	2 (13)	27 (5)	
	Type 2 diabetes	266 (51)	11 (73)	255 (50)	
	Other specified	25 (5)	0	25 (5)	
	Unknown	14 (3)	0	14 (3)	
Family history of diabetes		164 (31)	11 (73)	153 (30)	0.002
Previous history of DKA		133 (25)	2 (13)	131 (26)	0.123
Systolic blood pressure (mmHg)		122 ± 27	125 (110–145)	121 (105–140)	0.316
Pulse rate (beats/min)		105 ± 24	119 (96–127)	103 (87–120)	0.189
Body mass index (kg/m^2)		22.3 ± 5.1	22 (20–25)	21 (19–24)	0.178
HbA_{1c} (%)		11.2 ± 2.7	10.3 ± 2.5	11.3 ± 2.7	0.148
Glucose (mg/dL)		623 ± 323	413 (244–567)	554 (404–758)	0.006
Serum creatinine (mg/dL)		1.82 ± 1.52	1.3 (0.8–1.5)	1.4 (1.0–2.1)	0.199
Arterial blood gas test					
	pH	7.17 ± 0.15	7.19 (7.05–7.25)	7.18 (7.07–7.28)	0.624
	HCO_3 (mmol/L)	8.4 ± 5.6	4.8 (3.2–10.6)	7 (3.8–12.2)	0.358
	pCO_2 (mmHg)	20 ± 9	14 (11–24)	19 (12–27)	0.26
	pO_2 (mmHg)	117 ± 37	112 (100–136)	116 (97–133)	0.898
Anion gap		28.5 ± 9.0	30.2 ± 8.2	28.4 ± 9.1	0.441
Fasting C-peptide (ng/mL)		0.65 ± 0.84	0.6 (0.1–1.5)	0.3 (0.1–0.9)	0.659
Antihyperglycaemics					
	None	147 (26)	0	147 (29)	< 0.001
	Insulin	293 (56)	2 (13)	291 (57)	
	Only oral medications	83 (15)	13 (87)	70 (14)	
Precipitating factors[b]					
	Poor compliance	209 (40)	2 (13)	207 (41)	0.034
	Infection	154 (27)	3 (20)	131 (26)	0.77
	Alcohol drinking	94 (18)	3 (20)	91 (18)	0.74
	Caloric restriction	85 (16)	2 (13)	83 (16)	0.999
	Uncontrolled state[c]	343 (66)	7 (47)	336 (68)	0.095
	Pancreatitis	42 (8)	2 (13)	40 (8)	0.344
	Cardiovascular disease	16 (3)	0	16 (3)	0.999
	Miscellaneous	121 (23)	4 (27)	117 (23)	0.757
	Unknown	36 (7)	2 (13)	34 (7)	0.279
Presence of GAD antibody (yes)		149 (29)	3 (20)	146 (29)	0.662
Hospital stays (days)		10.8 ± 10.3	9 (6–15)	8 (6–12)	0.372
ICU stays (days)		2.5 ± 3.6	4 (2–6)	2 (0–3)	0.019
In-hospital mortality		16 (3)	0 (0)	16 (3.2)	0.999

Values are presented as means ± SD or as numbers (%) or medians (IQR).
LADA: latent autoimmunity diabetes in adults; GAD: glutamic acid; ICU: intensive care unit.
[a] Users vs. non-users by Mann–Whitney U, Student's t, chi-squared (χ^2) or Fisher's exact tests.
[b] Multiple precipitating causes of DKA.
[c] Uncontrolled state was defined as HbA1c ≥ 10 %.

the clinical characteristics of DKA in Korea, but those reports are now outdated and describe only specific types of DKA [3,8–10]. Recent epidemiological studies from England and the US suggest that, over the past 15 years, hospital admissions for DKA have increased, whereas the resulting mortality rates have decreased [1,11]. One study from Korea also showed that cases of DKA hospitalization had increased; however, these data were not nationwide [3].

The present study has followed the ADA definition of DKA [2]. However, random plasma glucose levels > 250 mg/dL were not included in our DKA criteria because SGLT2 inhibitor use is known to be associated with euglycaemic DKA [4]. In fact, our data have indicated that blood glucose concentration was < 250 mg/dL in 27% of SGLT2 inhibitor users with DKA. Given this new information, the need for updated diagnostic criteria was raised [12,13]. In addition, although the in-hospital mortality rate due to DKA in our study (3%) is higher than the 1% rate recently released by the US Centers for Disease Control and Prevention (CDC) [11], our mortality rate is still nonetheless markedly lower than previously found (12–13%); however, the definition of DKA differs from that used in previous Korean studies [8,14]. Furthermore, more than half the DKA episodes in our study were in patients with T2D, but such a large proportion may be because, in Korea, the frequency of T2D is greater than T1D compared with rates in other countries [15–17]. Moreover, Koreans with T2D have lower insulin secretory function than those with T2D of other ethnicities [18]. Finally, the prevalence of ketosis-prone T2D, the first manifestation of which is DKA, is as high in Korea as it is in the US [19].

SGLT2 inhibitors have a distinctive mechanism of action in that they lower plasma glucose levels by blocking proximal tubular glucose reabsorption. When treated with SGLT2 inhibitors, the insulin-to-glucagon ratio is lowered as insulin secretion is reduced in response to decreasing plasma glucose levels by glucosuria, whereas glucagon secretion increases through the direct stimulatory action of alpha cells [20,21]. This contributes to lipolysis in adipose tissue and ketogenesis in the liver, which can lead to enhanced circulating ketone bodies [7,22]. In animals, phlorizin (a non-selective SGLT1/SGLT2 inhibitor) decreased renal clearance of acetoacetate, which can increase ketonaemia [23]. In patients with

Table 2
Summary of cases of diabetes ketoacidosis (DKA) associated with sodium–glucose cotransporter-2 (SGLT2) inhibitor use.

Subjects	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age (years)	46	33	77	23	59	56	63	36	70	45	77	37	55	34	39
Gender	F	M	F	M	M	M	F	M	F	F	F	M	M	F	F
Body mass index (kg/m^2)	23.1	20.1	23.4	37.8	19.5	20.6	18.4	20.8	19.6	20.6	24.1	29.4	22.3	29.3	24.2
DM subtype	T1D	T2D	T2D	T2D	T2D	LADA	T2D	LADA	T2D	T1D	T2D	T2D	T2D	T2D	T2D
GAD antibodies	–	N/A	N/A	N/A	–	+	N/A	+	N/A	+	N/A	N/A	–	N/A	N/A
C-peptide in DKA	0.1	N/A	N/A	1.47	1.57	0.13	0.63	0.18	0.72	0.09	1.7	N/A	0.33	0.85	N/A
DM duration (years)	3	2	30	2	9	3	20	4	30	0	19	0	11	0	15
SGLT2 inhibitor	DAPA	DAPA	EMPA	DAPA	DAPA	DAPA	DAPA	EMPA	DAPA	DAPA	DAPA	DAPA	DAPA	EMPA	DAPA
Medication period (days)	7	N/A	5	380	N/A	290	N/A	112	106	13	N/A	20	68	N/A	248
Background medications	None	M	M	M	S/M	Insulin	D/M	S/M/D	D/M	S/M/D	S/M/D	D/M	M	S/M	Insulin/M
HbA_{1c} (%)	11	9.9	11.3	12.8	11.5	12.8	8.8	9	7.6	8.5	8.4	8.4	16.6	10.6	6.6
FPG (mg/dL)	244	698	361	493	433	597	274	413	359	182	567	234	434	855	178
sCr (mg/dL)	0.7	1.4	0.8	1.47	1.41	1.6	1.2	2.01	0.97	0.73	2.44	1.13	1.3	1.5	0.56
pH	7.34	7.21	7.12	7.22	7.25	7.06	7.19	7.05	7.01	6.88	7.4	7.2	7.05	7.15	7.256
HCO_3 (mmol/L)	16	4.2	7.4	4.8	10.6	3.4	8	2.2	3.2	1.5	12.1	9.4	3	4.7	13.3
Anion gap	26.3	32.8	29.1	35.2	33.4	42.6	35	43.8	32.8	34.5	21.9	29.6	20	23.3	13.3
Urine ketone	+	+	+	N/A	+	+	+	+	+	+	+	+	+	+	+
Serum ketone	+	+	+	+	+	+	+	N/A	+	+	N/A	N/A	N/A	N/A	+
Previous DKA	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Precipitating factors	None	PAN, NCWC	Infection	Overuse of glucose sweetener	Dehyd	Alcohol, NCWC	Infection	Alcohol, recent insulin discon	None	Calorie restriction	Infection	None	None	PAN, alcohol	Reduced insulin dose
Medications at discharge	MDI	Insulin + OHA	MDI	Insulin + OHA	MDI	MDI	MDI	MDI	MDI	MDI	Insulin + OHA	Insulin + OHA	OHA	MDI	Insulin + OHA

F: female; M: male; DM: diabetes mellitus; T1D/T2D: type 1/type 2 diabetes; LADA: latent autoimmune diabetes in adults; GAD: glutamic acid decarboxylase; N/A: not available; DAPA: dapagliflozin; EMPA: empagliflozin; M: metformin; S: sulphonylurea; D: dipeptidyl peptidase-4 inhibitor; FPG: fasting plasma glucose; sCr: serum creatinine; PAN: pancreatitis; NCWC: non-compliance with care; Dehyd: dehydration; discon: discontinuation; MDI: multiple daily injections (insulin); OHA: oral hypoglycaemic agent.

diabetes, ketone bodies in the blood of those treated with SGLT2 inhibitors increased by as much as several times compared with control groups [24–26]. In fact, raised levels of circulating ketone bodies have emerged as a potential mechanism of cardioprotection, as demonstrated with empagliflozin in the EMPA-REG trial, in which beta-hydroxybutyrate used as an energy source improved cardiac efficiency [27].

Nevertheless, while mild hyperketonaemia in patients treated with SGLT2 inhibitors appears to be beneficial for the cardiovascular system, doubts remain as to the increased risk of DKA caused by SGLT2 inhibitors. One claims database in the US has suggested that SGLT2 inhibitors are associated with an increased risk of DKA compared with dipeptidyl peptidase (DPP)-4 inhibitors [28]. In addition, a meta-analysis of randomized controlled trials as well as results from claims databases and national registries have reported a clinically insignificant risk of DKA associated with SGLT2 inhibitor treatment [29–32]. Although our present study can provide no information on whether or not SGLT2 inhibitors increased the risk of developing DKA, it has revealed that even if users of SGLT2 inhibitors showed lower plasma glucose levels at DKA presentation, they required longer ICU care; overlooked or delayed diagnoses of DKA in SGLT2 inhibitor users may explain DKA events requiring longer-term intensive care [33]. However, given the limited number of DKA episodes (n = 15) associated with SGLT2 inhibitors and the characteristic differences between both our study groups, further research is still needed to determine the effects of SGLT2 inhibitors on the clinical course of DKA treatment. Also, to minimize DKA episodes associated with SGLT2 inhibitors, prescribing these agents should be avoided in DKA-prone patients, including those with T1D, diabetes-related autoimmunity such as LADA and those with a previous history of DKA. If patients are under DKA-precipitating conditions, including infections and pancreatitis, then stopping SGLT2 inhibitor treatment should be considered.

In conclusion, our study has investigated the clinical characteristics and outcomes of DKA in Korean patients, and found that DKA episodes associated with SGLT2 inhibitor use are rare, but require longer durations of intensive treatment compared with SGLT2 inhibitor non-users. Thus, when prescribing SGLT2 inhibitors, physicians should ensure that they select subjects properly, and should also consider informing patients of any DKA-precipitating conditions and DKA-related symptoms.

Contributors

All authors participated in collecting the data and in the discussion, and reviewed the manuscripts. J.Y.J. contributed to the statistical analyses and writing the manuscripts. D.J.K. is the guarantor of this work and, as such, had full access to all the data in the study and so takes responsibility for the integrity of the data and accuracy of the data analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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