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단일기관에서 경험한 소아 당뇨 케토산증의 고찰

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Clinical and Laboratory Characteristics of Pediatric Diabetic Ketoacidosis: A Single-Center Study

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Abstract

Background: Diabetic ketoacidosis (DKA) is an acute complication of pediatric type 1 diabetes mellitus (T1DM). We aimed to determine the risk factors and clinical characteristics of children and adolescents with DKA.

Methods: We retrospectively evaluated 59 episodes of DKA in 43 patients who were hospitalized for DKA between January 2006 and December 2015. DKA was classified as mild, moderate, or severe, according to patient history of DKA. The clinical and laboratory characteristics of these subgroups were compared.

Results: The average patient age was 11.98 ± 4.40 years (range, 1.3~17.9 years). Moderate episodes were the most common, with 21 episodes (35.6%), followed by 19 severe (32.2%) and 19 mild episodes (32.2%). Significant differences were observed between the subgroups regarding their characteristics of aggravated. Severe DKA episodes were more often observed during the winter season. Recurrent DKA cases were determined in 31 episodes (52.5%) who were significantly older, had higher body mass index, and lower serum C-peptide levels than the newly diagnosed DKA group. Female patients experienced severe and moderate cases more frequently (P = 0.041), which included two deaths. Only blood glucose

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levels were significantly higher in these fatal cases (P = 0.022).
Conclusion: Even among the patients who had previously experienced DKA and older children with low serum C-peptide levels, there was no reduction in the severity of DKA. We recommend that patients with DKA be carefully treated and continuously informed regarding the importance of maintaining proper blood glucose levels, regardless of their previous history of DKA, age, or regularity of insulin therapy.

Keywords: Child, Diabetic ketoacidosis, Diabetes mellitus, Type 1

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most serious pediatric endocrine diseases; it is caused by destruction of insulin-producing beta cells in the pancreas. Diabetic ketoacidosis (DKA) is a common acute complication of T1DM; although the metabolic changes associated with DKA typically occur within 24 hours, the symptoms may last for several days. These symptoms include polydipsia, polyuria, polyphagia, weight loss, vomiting, abdominal pain, and altered consciousness [1]. In addition, the physical manifestations of DKA include reduced skin turgor, Kussmaul respiration, bradycardia, and shock. Unfortunately, 60~80% of DKA cases occur in children with T1DM, and 5~20% of these cases eventually relapse [2,3].

According to a recent study, the number of DKA cases in adults has rapidly increased over the previous 20 years [4]. Lee et al.[1] reported that poor glycemic control is the most common factor for DKA and prevention of DKA is possible with medical care, proper education, and effective communication with a health care provider. Especially, in school vacation seasons, control of blood glucose levels and insulin injections are loosened, and infection is common. This study aimed to analyze the pattern of DKA with the goal of improving future patient management strategies.

In Western countries, the incidence of DKA is relatively high, ranging from 4.6 to 8.0 cases per 1,000 patients with diabetes [5-7]. Furthermore, 7.6% of patients who are hospitalized due to DKA receive intensive care; mortality rates of 5~13% have been reported in this population [8,9]. Therefore, greater understanding of DKA in children with T1DM is needed in order to reduce mortality rates and associated health care costs.

This study analyzed the clinical/laboratory characteristics and seasonal variations of DKA, based on the severity of T1DM in children and adolescents at the time of admission in a single center.

MATERIALS AND METHODS

1. Subjects

From January 2006 and December 2015, T1DM patients who were diagnosed with DKA and received follow-up care at the Department of Pediatrics, Chonbuk National University Children's Hospital were

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included in the study. The diagnostic criteria included the following: metabolic symptoms such as polydipsia, polyuria, polyphagia, and weight loss; the presence of sugar and ketone in the urine; random blood glucose levels of ≥ 300 mg/dL; arterial blood acidosis (pH < 7.3 or bicarbonate < 15 mEq/L) [10]; and age < 18 years at the time of admission.

Informations on age, sex, and body mass index (BMI) were collected upon admission. The levels of blood glucose, glycated hemoglobin (HbA1c), serum C-peptide, serum insulin, pancreatic enzymes (amylase and lipase), and serum bicarbonate (HCO_3^-) were measured. In addition, the corrected serum sodium levels ([(glucose [mg/dL] - 100) × 0.016] + serum Na [mg/dL]) and effective serum osmolality ([2 × (Na + K)] + [blood urea nitrogen, BUN (mg/dL) / 2.8]+[glucose (mg/dL) / 18]) were obtained. The level of anti-glutamic acid decarboxylase antibody was measured using an immunoradiometric assay (RSR Ltd., Cardiff, UK). Concentrations of insulin autoantibodies and islet cell autoantigen 512 were not measured in all patients due to economic reasons.

Based on the diagnostic criteria, 63 episodes of DKA were confirmed in 47 patients. Four cases in four patients were excluded for the following reasons: serum C-peptide levels of > 1.0 ng/mL during an observation period of > 6 months in three cases, and inaccurate follow-up data in one case. Finally, we performed a retrospective analysis of the medical records for 59 cases in 43 patients. All cases were classified by severity according to the degree of acidosis, as described in the International Society for Pediatric and Adolescent Diabetes guidelines [10,11]: mild, serum 7.2 ≤ pH < 7.3 or 10 mEq/L ≤ bicarbonate < 15 mEq/L; moderate, serum 7.1 ≤ pH < 7.2 or 5 mEq/L ≤ bicarbonate < 10 mEq/L; and severe, serum pH < 7.1 or bicarbonate < 5 mEq/L. The patients were assessed by recurrent DKA state (newly diagnosed and recurrent DKA groups). The newly diagnosed group included patients who were diagnosed with T1DM and DKA at the same time. The recurrent DKA group included patients with DKA who were already diagnosed with T1DM with a prior history of DKA, and also had insulin treatment for more than six months.

In addition, comparisons of the DKA cases were performed by seasonal distribution: spring (March~May), summer (June~August), autumn (September~November), and winter (December ~February). Furthermore, depending on the patient's sex and the status of the DKA case as recurrent or newly diagnosed at admission, a comparative analysis according to age was also performed. The Institutional Review Board of Chonbuk National University Hospital approved this study (CUH 2017-08-018).

2. Statistical methods

Statistical processing and data analysis were conducted using PASW Statistics ver. 18.0 for Windows (IBM Co., Armonk, NY, USA). For the comparison of clinical parameters according to DKA severity by arterial blood pH levels, analysis of variance (ANOVA) with Tukey's post-hoc tests was performed. The chi-square test was used to compare severity and seasonal distribution of DKA. Clinical parameters were compared according to survival status and DKA status (newly diagnosed or recurrent) by independent t-test. A P-value < 0.05 was considered significant.

RESULTS

1. Clinical features of DKA in severity subgroup

A total of 59 episodes (20 episodes in male patients and 39 episodes in female patients) in 43 patients (16 boys and 27 girls) were evaluated. The average patient age was 11.98 ± 4.40 years (range, 1.3~17.9 years), and 25.4% of the DKA episodes occurred in patients aged < 10 years old. The DKA episodes were classified as mild in 19 episodes (32.2%), moderate in 21 (35.6%),

Table 1. Comparison of the clinical and laboratory characteristics of patients with diabetic ketoacidosis

Characteristic	Total (n = 59, 100.0%)	Mild DKA (n = 19, 32.2%)	Moderate DKA (n = 21, 35.6%)	Severe DKA (n = 19, 32.2%)	*P*-value
Age (y)	11.98 ± 4.40 (1.3~17.9)	11.19 ± 5.09 (1.3~17.9)	11.85 ± 4.60 (2.8~17.1)	12.91 ± 3.36 (6.7~17.9)	0.484
Sex					0.041*
Male	20	10	6	4	
Female	39 (66.1)	9 (47.4)	15 (71.4)	15 (78.9)	
BMI (kg/m^2)	17.37 ± 3.66	17.51 ± 4.66	17.12 ± 3.02	17.50 ± 3.34	0.929
In-hospital mortality	2 (3.4)	0 (0.0)	1 (4.8)	1 (5.3)	0.374
Newly diagnosed DKA cases	28 (47.5)	8 (42.1)	11 (52.4)	9 (47.4)	0.747
Recurrent episodes	31 (52.5)	11 (57.9)	10 (47.6)	10 (52.6)	
Duration of T1DM in recurrent episodes (y)	3.83 ± 3.15 (0.5~9.5)	4.08 ± 3.20 (1.5~9.4)	4.00 ± 3.49 (0.6~9.5)	3.38 ± 3.17 (0.5~8.9)	0.924
Arterial pH	7.13 ± 0.12	7.26 ± 0.04^a	7.15 ± 0.03^b	6.99 ± 0.08^c	0.000**
Plasma glucose level (mg/dL)	563.74 ± 147.01	492.00 ± 149.84^a	593.80 ± 141.02^{a,b}	603.84 ± 130.16^b	0.031*
Fasting serum C-peptide (ng/mL)	0.36 ± 0.40	0.38 ± 0.53	0.37 ± 0.36	0.31 ± 0.30	0.858
GADA level (normal range ≤ 0.9 U/mL)	26.93 ± 38.41	23.47 ± 29.98	24.92 ± 30.14	32.77 ± 54.51	0.836
GADA positivity	45 (76.3)	12 (63.2)	18 (85.7)	15 (78.9)	0.233
HbA1c (%)	12.88 ± 2.38	12.17 ± 2.78	12.79 ± 1.87	13.68 ± 2.33	0.144
Serum creatinine (mg/dL)	0.98 ± 0.34	0.91 ± 0.25	1.01 ± 0.26	1.03 ± 0.48	0.511
Anion gap	28.86 ± 9.54	25.23 ± 10.42	30.28 ± 7.41	30.91 ± 10.53	0.203
Corrected serum Na level (mg/dL)	141.84 ± 5.90	141.11 ± 4.50^{a,b}	139.20 ± 5.10^b	145.55 ± 6.40^a	0.002**
Effective serum osmolality (mOsm/kg)	300.17 ± 12.78	297.02 ± 10.77^{a,b}	295.59 ± 10.56^a	308.58 ± 13.43^b	0.002**

Values were obtained at the time of diagnosis and are presented as mean ± SD (range), number only, number (%), or mean ± SD only.
DKA, diabetic ketoacidosis; BMI, body mass index; T1DM, type 1 diabetes mellitus; GADA, anti-glutamic acid decarboxylase antibody; HbA1c, glycated hemoglobin; SD, standard deviation.
The superscript letters indicate significant differences between groups identified by Tukey's multiple comparison test.
* $P < 0.05$, ** $P < 0.01$.

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or severe in 19 (32.2%) based on blood acidity, which was evaluated via arterial blood gas analysis. The proportion of female patients was higher in the severe DKA group (P = 0.041). The average BMI was 17.37 ± 3.66 kg/m^2, and no significant differences in BMI were observed between the three groups (P = 0.929). Twenty-eight DKA episodes were newly diagnosed (47.5%), whereas 31 episodes were recurrent (52.5%), although no differences in incidence were observed among the DKA severity groups (P = 0.747, Table 1). Two patients experienced five episodes of DKA, and one patient experienced four such episodes. In addition, five patients experienced two episodes of DKA, and seven patients experienced one episode. A mechanical ventilator was used in three episodes, and two patients died. The two deceased patients belonged to the moderate and severe DKA groups (Table 1).

2. Laboratory characteristics of the DKA episodes

There were significant differences among the three DKA groups regarding their average plasma glucose levels (P = 0.031). The severe group had the highest plasma glucose (603.84 ± 130.16 mg/dL), corrected serum sodium (145.55 ± 6.40 mg/dL, P = 0.002), and serum effective osmolality (308.58 ± 13.43 mOsm/kg, P = 0.002).

However, no other inter-group differences were observed. Interestingly, no significant differences in the mean HbA1c levels were observed among the DKA groups (Table 1).

3. Laboratory characteristics of the experienced DKA episodes

The mean age (P = 0.004) and BMI (P = 0.030) were significantly increased, and fasting serum

Table 2. Characteristics of the diabetic ketoacidosis patients according to status of recurrence

Characteristic	Newly diagnosed DKA	Recurrent DKA	*P*-value
Number of episodes	28	31	
Recurrence of DKA (number of episodes/patients)		5/2, 4/1, 2/5, 1/7	
Patients (male/female)	28 (11/17)	15 (5/10)	0.752
Duration of T1DM (y)		3.83 ± 0.72 (0.5~9.5)	
Age (y)	10.39 ± 4.60 (1.3~17.8)	13.56 ± 3.59 (6.2~17.9)	0.004**
BMI (kg/m^2)	16.39 ± 3.49 (12.00~24.42)	18.45 ± 3.65 (12.70~27.23)	0.030*
Plasma glucose (mg/dL)	587.72 ± 110.22	535.93 ± 173.46	0.178
HbA1c (%)	12.69 ± 2.48	13.08 ± 2.27	0.530
Arterial pH	7.14 ± 0.12	7.12 ± 0.13	0.616
Fasting serum C-peptide (ng/mL)	0.55 ± 0.45	0.18 ± 0.28	0.001

Values are presented as number only, mean ± SD (range), or mean ± SD only.
DKA, diabetic ketoacidosis; T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated hemoglobin; SD, standard deviation.
Statistical significance was determined using the independent t-test.
* P < 0.05, ** P < 0.01.

C-peptide levels (P = 0.001) decreased in the recurrent DKA group. However, plasma glucose level, HbA1c level, and arterial pH were not significantly different between patients with newly diagnosed DKA and those with recurrent DKA (Table 2).

4. Seasonal trends in DKA incidence

The incidence of DKA differed significantly between the seasons (P = 0.001, Fig. 1A) and was highest in summer (20 episodes, 33.9%), followed by autumn (16 episodes, 27.1%), winter (15 episodes, 25.4%), and spring (8 episodes, 13.6%). The severe group had the highest number of episodes in the winter, while the mild group had the highest number of episodes in the spring. The proportion of moderate episodes was highest in the summer and fall. The number of newly diagnosed DKA episodes (n = 28, Fig. 1B) was highest in the autumn (10 episodes, 35.7%), followed by the winter (8 episodes, 28.6%), summer (6 episodes, 21.4%), and spring (4 episodes, 14.3%). The seasonal rate did not differ significantly (P = 0.307), although the greatest number of 31 DKA episodes were observed in summer (14 episodes, 45.2%), followed by winter (7 episodes, 22.6%), autumn (6 episodes, 19.4%), and spring (4 episodes, 12.9%).

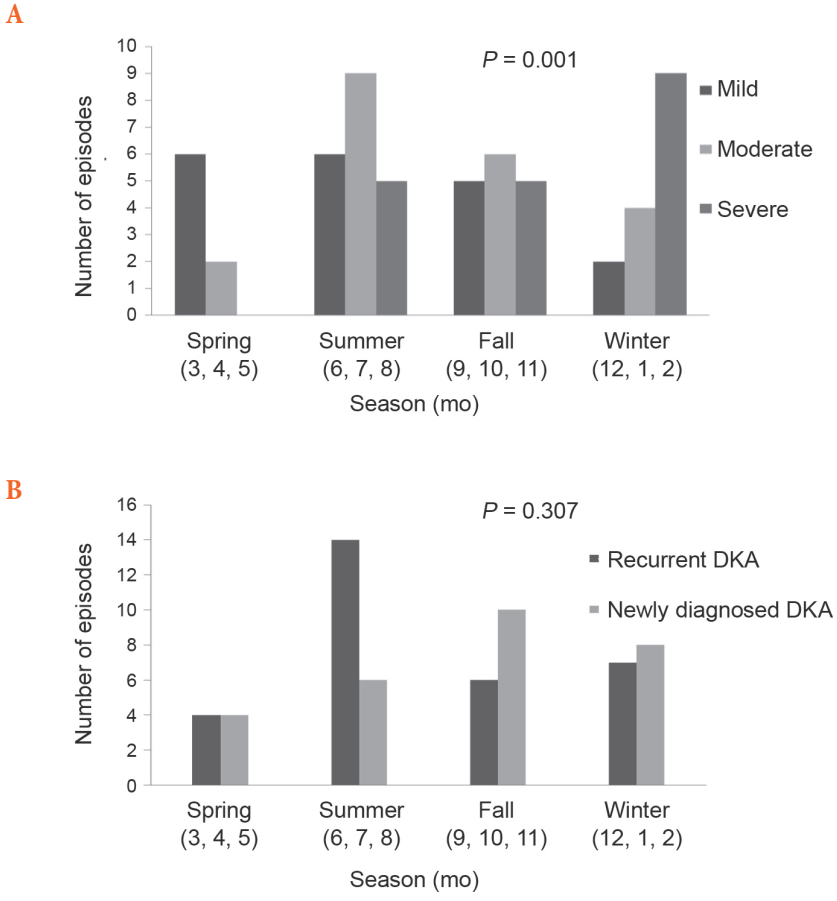

Fig. 1. Seasonal distribution of diabetic ketoacidosis severity (A) and prior diabetic ketoacidosis history (B) on the day of admission. Months are numbered from 1~12 for January~December, respectively.
DKA, diabetic ketoacidosis.

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5. Mortality and features of DKA

Among the 59 episodes we examined, two episodes were fatal (occurring in November and October). Both deceased patients were female, and were 13.4 and 11.2 years old. Related symptoms included cold sensations prior to admission, and the patients had normal serum amylase and lipase levels. The first deceased patient had previously been diagnosed with T1DM, and had received insulin treatment for 4.7 years. At her second and last admission, she appeared very sick and drowsy, and was classified as having severe DKA (pH 6.8 and HbA1c level of 15.5%). Prior to the admission, she had exhibited poor compliance with her insulin therapy and instructions regarding exercise and food intake. Brain computed tomography was performed, which revealed pre-existing hydrocephalus and a suspicious edematous cerebral lesion. The second deceased patient had no history of diabetes, although she was simultaneously diagnosed with T1DM and moderate DKA (pH 7.13 and HbA1c level of 13.5%). Brain computed tomography also revealed signs suggestive of cerebral edema (Table 3). Both episodes were associated with significantly higher blood glucose levels (793.00 ± 280.01 mg/dL, $P = 0.022$) at the time of admission compared to the survivors. However, no differences were observed in age or HbA1c, blood urea nitrogen, serum creatinine, HCO_3^-, and arterial blood pH levels when the deceased

Table 3. Characteristics of the patients with fatal diabetic ketoacidosis

Characteristic	Patient no. 1	Patient no. 2
Sex	Female	Female
Age (y)	13.4	11.2
BMI (kg/m^2)	25.3	12.0
Duration of symptoms (d)	2	7
Month of DKA occurrence	November	October
Associated disease/symptom	(–)/Flu-like symptom(+)	(–)/Flu-like symptom(+)
Duration of T1DM (y)	4.7	0
Prior history of DKA	No	No
Arterial pH	6.80	7.13
Anion gap	16.5	13.5
Plasma glucose (mg/dL)	991	595
HbA1c (%)	15.5	13.5
GADA	No	Yes
Fasting serum		
C-peptide (ng/mL)	0.01	0.2
Amylase/lipase (IU/L)	20/16	86/53
Brain CT findings	Severe hydrocephalus, cerebral edema(+)	Cerebral edema(+)
Respected cause	Irregular insulin injection	–

BMI, body mass index; DKA, diabetic ketoacidosis; T1DM, type 1 diabetes mellitus; HbA1c, glycated hemoglobin; GADA, anti-glutamic acid decarboxylase antibodies; CT, computed tomography.

patients and survivors were compared (Table 4).

DISCUSSION

Globally, T1DM annually affects 65,000 children who are ≤ 15 years old, and this prevalence increases by 3% per year [12,13]. Approximately 10~70% of these patients experience DKA [14], which, in children, may be accompanied by life-threatening complications such as cerebral edema. Kim et al. reported that the number of patients who are diagnosed with T1DM has increased over the past 26 years, and that increasing numbers of DKA cases are discovered at the time of the diabetes diagnosis [15]. Combinations of fluids and insulin are used to treat DKA, and diverse expertise is needed to diagnose and treat DKA because the clinical manifestations at admission may range from very mild to severe (with varying degrees of treatment necessary). Factors that contribute to the incidence of DKA include poorly metabolic control [16] and a rapid decrease in pancreatic beta cell function [17]. In a recent study, age under 12 years, lower serum C-peptide level, preceding infection, and delayed diagnosis were strongly related to DKA; and severe DKA was increased in situations where there was limited parental education level and a prior episode of infection [18].

Regarding sex, one study has reported that sex did not significantly relate to the incidence or clinical characteristics of DKA [19]. In our study, we observed that prevalence and severity of DKA were higher

Table 4. Characteristics of the diabetic ketoacidosis patients according to survival status

Characteristic	Surviving	Deceased	*P*-value
Number of episodes/patients	57/41	2/2	
Age (y)	12.02 ± 4.45	12.30 ± 1.56	0.930
BMI (kg/m^2)	17.42 ± 3.54	18.65 ± 9.40	0.883
Plasma glucose (mg/dL)	553.26 ± 137.76	793.00 ± 280.01	0.022*
HbA1c (%)	12.84 ± 2.38	14.50 ± 1.41	0.332
Serum creatinine (mg/dL)	0.96 ± 0.34	1.39 ± 0.29	0.089
HCO_3^- (mmol/L)	7.65 ± 5.09	6.00 ± 4.53	0.653
Anion gap	29.47 ± 9.28	15.00 ± 2.12	0.034*
Arterial pH	7.14 ± 0.12	6.97 ± 0.23	0.050
AST (IU/L)	24.11 ± 12.51	19.00 ± 1.41	0.569
ALT (IU/L)	21.44 ± 11.29	18.00 ± 4.24	0.671
Amylase (IU/L)	84.60 ± 148.62	53.00 ± 46.67	0.768
Lipase (IU/L)	59.49 ± 120.50	34.50 ± 26.16	0.774
Fasting serum C-peptide (ng/mL)	0.38 ± 0.42	0.11 ± 0.13	0.358
GADA (U/mL)	25.95 ± 38.55	30.19 ± 42.44	0.881

Values are presented as number only or the mean ± standard deviation.

BMI, body mass index; HbA1c, glycated hemoglobin; HCO_3^-, bicarbonate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GADA, anti-glutamic acid decarboxylase antibodies.

Statistical significance was determined using the Mann-Whitney U-test.

* $P < 0.05$.

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among female patients. Younger age (< 2 years old) in children with T1DM is associated with an increased risk of severe DKA [20]. Unfortunately, it is unclear why severe DKA manifests in certain young patients; the factors that predict its severity are also unclear. Therefore, it is important to clarify the relationships between patient characteristics and DKA in order to select effective treatment for control of diabetes. The current study determined that there was no significant difference between disease severity and frequency of recurrence in young patients (< 10 years old), although newly diagnosed cases of DKA were common in this age group. However, we observed significantly more relapse episodes in patients who were ≥ 10 years old, which is likely related to the increasing incidence of DKA with increasing illness duration.

Serum acidity was strongly correlated with blood glucose levels ($r = -0.414$, $P = 0.001$). This result indicates that blood sugar level is the most important factor in determining the risk of acute complications; DKA patients with diabetes should be educated regarding related conditions, especially the effects of hyperglycemia. Despite increased understanding and medical advancements in the field of diabetes treatment, the incidence of DKA was constant among patients in the current study, regardless of DKA history. Unfortunately, confirmed diagnoses of DKA were common in patients with a history of DKA. In addition, HbA1c levels, sex, blood pH level at admission, and plasma glucose levels were not different between newly diagnosed and recurrent DKA cases. Only recurrent DKA cases were associated with older age, lower serum C-peptide levels, and higher BMI than the newly diagnosed DKA group. Therefore, physicians should focus on the early identification and prevention of DKA, even with administration of insulin therapy, in older children and adolescents with low serum C-peptide levels.

Kalliora et al.[21] reported that cold seasons were associated with islet cell damage by viral infection and autoimmune response. However, others reported that spring or summer seasons were associated with diabetes [22]. In a Korean report, DKA was distributed evenly by season, due to poor blood glucose control and infection [1]. In our study, we found that moderate cases were more common in summer, while severe cases were more common in winter. In addition, recurrent DKA cases were more frequent in summer, while the number of newly diagnosed and recurrent cases was similar in winter. Thus, blood glucose levels appear to be unstable in the summer and winter, and appropriate follow-up and management of blood glucose levels is critical among patients who are already receiving treatment for DKA, especially in the summer. The severe cases are most common in the winter season. Thus, enhanced education and blood sugar management are needed in that season. This study did not explore the effects of accompanying infectious diseases. More research in this area is needed.

The prevalence of DKA-associated mortality has been reported to be approximately 1~2% [23]. In our study, both the deceased patients presented with neurological symptoms at admission that progressed to coma within 24 hours, and cerebral edema was identified as the cause of death in both cases. Unfortunately, the mortality rate associated with neurological symptoms has been reported to be as high as 90% [24]. Neurological exacerbation after DKA therapy typically occurs within 24 hours after the completion of treatment, while the biochemical and

clinical manifestations are improving. Our first fatal DKA case occurred during insulin therapy (4.7 years after a diagnosis of T1DM), while the second case occurred simultaneously with the diagnosis. Therefore, DKA episodes should be treated prudently. In these cases, it is important to predict the incidence of DKA and provide appropriate fluid and insulin therapy. Furthermore, when neurological abnormalities are observed, immediate radiological examination should be performed.

The current study had some limitations. First, the research was carried out retrospectively at a single center. Thus, it involved a small sample size and small number of findings. Second, it was not possible to analyze DKA-related factors in the recurrent DKA group, such as insulin compliance, comorbidities, and diabetic educational status.

In conclusion, we showed that DKA was more severe in female patients than in male patients. In addition to the higher incidence of moderate DKA during the summer, DKA occurred most frequently in T1DM patients who had a history of DKA. The severe group did not have the following characteristics: younger age, lower weight, newly diagnosed DKA, and higher HbA1c levels. Furthermore, there was no significant difference in the HbA1c levels of the newly diagnosed cases vs. recurrent cases of DKA, indicating that perpetual and aggressive treatment (including education, proper insulin dosing, and blood sugar management) is needed, even in patients who are currently receiving treatment for DKA, including adolescents.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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