

[ORIGINAL ARTICLE]

Clinical Characteristics Associated with the Development of Diabetic Ketoacidosis in Patients with Type 2 Diabetes

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Abstract:

Objective This study analyzed the clinical and laboratory parameters that might influence the clinical outcomes of patients with type 2 diabetes who develop diabetic ketoacidosis (DKA), which has not been well investigated.

Methods We reviewed the clinical and laboratory data of 158 patients who were hospitalized due to DKA between January 2006 and June 2019 and compared the data of patients stratified by the type of diabetes. In addition, the patients with type 2 diabetes were subdivided according to age, and their clinical and laboratory findings were evaluated.

Results Patients with type 2 diabetes had a longer symptom duration associated with DKA, higher body mass index (BMI), and higher C-peptide levels than those with type 1 diabetes ($p < 0.05$). Among patients with type 2 diabetes, elderly patients (≥ 65 years old) had a longer duration of diabetes, higher frequency of DKA onset under diabetes treatment, higher effective osmolality, lower BMI, and lower urinary C-peptide levels than nonelderly patients (< 65 years old) ($p < 0.05$). A correlation analysis showed that age was significantly negatively correlated with the index of insulin secretory capacity.

Conclusion Patients with DKA and type 2 diabetes had a higher BMI and insulin secretion capacity than those with type 1 diabetes. However, elderly patients with type 2 diabetes, unlike younger patients, were characterized by a lean body, impaired insulin secretion, and more frequent DKA development while undergoing treatment for diabetes.

Key words: diabetic ketoacidosis, type 2 diabetes, C-peptide, elderly

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Introduction

Diabetic ketoacidosis (DKA) is an acute form of metabolic failure caused by insulin deficiency (1, 2). Epidemiological studies have indicated that hospitalizations due to DKA are increasing annually (3-6), and this situation is associated with increasing healthcare costs (7). Given that DKA is potentially life-threatening but largely preventable (3), analyzing the clinical and biochemical features associated with DKA may have significant implications on the

patient care and healthcare expenditure.

Hospital admissions for DKA are more common among those with type 1 diabetes than those with type 2 diabetes. However, admissions due to DKA in patients with type 2 diabetes are increasing (3). Previous observational studies have compared the characteristics of DKA in patients with type 1 and type 2 diabetes (8-10). However, the symptoms of DKA have not been compared in detail stratified by the types of diabetes (11). Furthermore, aging has been recognized as a poor prognostic factor in patients with DKA (12). Although the prevalence of DKA in elderly patients has

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been reported (13), the clinical and biochemical characteristics of DKA remain unclear. Given that the number of older individuals with diabetes in Japan is rising (14), it is important to evaluate the characteristics of DKA among elderly patients. Nevertheless, previous studies have assessed relatively young Japanese patients, mainly those with type 1 diabetes (8, 15).

Therefore, in the present study, we evaluated the characteristics of DKA among patients with type 2 diabetes, stratified by age, to gain a different perspective.

Materials and Methods

Study design and population

This retrospective observational study recruited patients with DKA who were admitted to Yokohama City Minato Red Cross Hospital between January 2006 and June 2019. All procedures complied with the ethical standards set by the committee on human experimentation (institutional and national) and were performed in accordance with the principles of the 1964 Declaration of Helsinki and later versions. The human ethics committee of Yokohama City Minato Red Cross Hospital approved the study.

Patients

DKA was determined by plasma glucose levels ≥ 250 mg/dL (13.9 mmol/L), presence of ketonemia (positive urinary ketones or increased blood ketone bodies), and metabolic acidosis [blood pH ≤ 7.30 or bicarbonate ion (HCO_3^-) ≤ 18 mEq/L]. Euglycemic DKA was defined as the presence of ketonemia and metabolic acidosis without hyperglycemia (plasma glucose < 250 mg/dL). Type 1 and type 2 diabetes were diagnosed according to the guidelines of the American Diabetes Association (16). Type 2 diabetes was diagnosed in individuals who were negative for glutamic acid decarboxylase antibody (GAD-Ab) and met at least 1 of the following 2 criteria: presence of endogenous insulin secretion (serum C-peptide levels ≥ 0.6 ng/mL or urinary C-peptide levels ≥ 20 $\mu\text{g/day}$), and/or managed diabetes without exogenous insulin during the course of the treatment. Patients under 18 years old on admission, and with diabetes of unknown type were excluded. In addition to patients with a confirmed diagnosis of type 2 diabetes based on the criteria described above, patients diagnosed with type 1 diabetes were recruited as the control group.

The evaluation of clinical and laboratory data

Clinical and laboratory data to identify DKA were collected from the medical records prepared during hospitalization. Clinical data, including the age, sex, body mass index (BMI), duration of diabetes, type of diabetes, presenting symptoms, symptoms' duration, triggers for DKA, history of recurrent DKA, and patient outcomes, were collected. The duration of diabetes was estimated from the first indication of hyperglycemia during a medical examination, diagnosis

of diabetes, or initiation of treatment for hyperglycemia at a medical institution. We defined thirst, polydipsia, polyuria, and weight loss as hyperglycemic symptoms and abdominal pain, nausea, and vomiting as abdominal symptoms for hyperglycemia. We classified the treatment status of diabetic patients until admission due to DKA into the following three categories: "under treatment" for patients who were undergoing treatment up to admission due to DKA; "untreated or self-interrupted treatment" for patients who were diagnosed with diabetes but neglected or self-interrupted the treatment; and "newly diagnosed" for patients who were diagnosed with diabetes for the first time on admission due to DKA.

We also collected laboratory data at the time of admission, including levels of plasma glucose, glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), serum C-peptide, urinary C-peptide, several electrolytes, pH, 3-beta-hydroxybutyric acid, HCO_3^- , and effective osmolality. The eGFR was calculated using the following equation: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$, for women) (17). Fasting serum C-peptide levels, 24-hour urinary C-peptide levels, and body weight were measured after hyperglycemia and ketosis had been improved with the initial treatment. The serum C-peptide immunoreactivity index (CPR index) and secretory units of islets in transplantation index (SUIT index) were calculated using the following equations: $\text{CPR index} = \text{fasting serum C-peptide} / \text{fasting plasma glucose}$, and $\text{SUIT index} = 1,500 \times \text{fasting serum C-peptide} / (\text{fasting plasma glucose} - 61.7)$ (18). Effective osmolality was calculated using the following equation: $\text{effective plasma osmolality (mOsm/L)} = \text{serum sodium} \times 2 + \text{plasma glucose} / 18$. In patients who had undergone a venous blood gas analysis only at the time of admission, the pH of the venous blood gas was increased by 0.03, and HCO_3^- was decreased by 1.0, as mentioned in a previous study (19).

Statistical analyses

Clinical and laboratory data are presented as the means \pm standard deviations or medians and interquartile ranges (IQRs; first and third quartiles). Patients were stratified into two groups according to the type of diabetes, and those with type 2 diabetes were subdivided according to age (≥ 65 vs. < 65 years old). The differences between groups were analyzed using Student's *t*-test, the Mann-Whitney U-test, and Fisher's exact test, as appropriate. Spearman's correlation coefficients were calculated to evaluate the relationship between two nonparametric values. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (20).

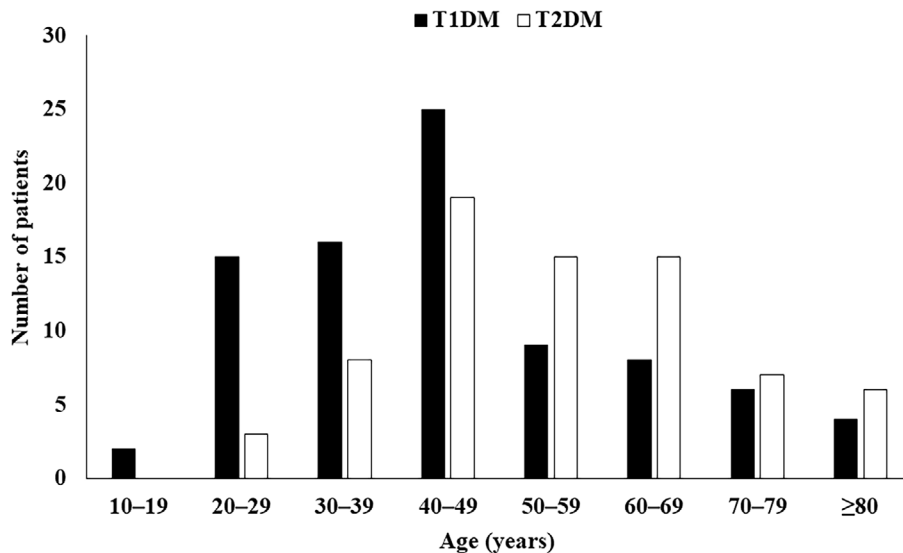


Figure. Distribution of the age at the time of admission for patients with type 1 and type 2 diabetes. The numbers of patients are individually shown for each type of diabetes. T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

Results

Characteristics of DKA patients with type 1 and type 2 diabetes

We identified 171 patients with DKA during the study period. Two patients under 18 years old were excluded; 6 patients were excluded due to a lack of data on islet cell antibodies; and 5 patients were excluded as the type of diabetes could not be determined because neither data about endogenous insulin secretion nor an accurate clinical history of insulin treatment before DKA onset, were available. Of the remaining 158 adult patients with DKA, 73 had type 2 diabetes, and 85 had type 1 diabetes, including 1 patient with euglycemic DKA. According to the medical records, no patient was using steroids or other drugs that cause drug-induced hyperglycemia. All DKA patients with type 2 diabetes were negative for GAD-Ab. Overall, one patient who had type 2 diabetes with DKA died. The age at the time of admission for those with type 1 and type 2 diabetes was widely distributed, with the oldest age being 97 years (Figure). Most patients with type 2 diabetes were in the age group of 40-60 years ($n=49$, 67.1%); conversely, those with type 1 diabetes were mostly in the age group of 20-40 years ($n=56$, 65.9%).

Table 1 shows the clinical and laboratory findings of patients with DKA with type 2 and type 1 diabetes. Nausea and vomiting were the major abdominal symptoms in both groups. A lower rate of prevalence of abdominal symptoms, longer symptoms' duration, and higher BMI were observed in patients with type 2 diabetes than in those with type 1 diabetes ($p<0.05$). Furthermore, higher levels of serum and urinary C-peptide, pH, and HCO_3^- were observed in patients with type 2 diabetes. With respect to the cause of the devel-

opment of ketoacidosis, the percentage of patients who discontinued treatment was similar in both groups. Of the patients with recurrent DKA among those with type 1 diabetes, two were hospitalized four times, two were hospitalized thrice, and three were hospitalized twice; among those with type 2 diabetes, one patient was hospitalized four times, one was hospitalized thrice, and three were hospitalized twice. Among all participants, the pre-hospital treatment status of two participants could not be confirmed. Among patients with type 2 diabetes who continued the treatment, the following antidiabetic agents were given on admission: sulfonylurea ($n=2$, 2.7%), biguanide ($n=4$, 5.5%), dipeptidyl peptidase 4 inhibitor ($n=6$, 8.2%), glinide ($n=2$, 2.7%), α -glucosidase inhibitor ($n=3$, 4.1%), sodium-glucose cotransporter 2 inhibitor (SGLT2i) ($n=2$, 2.7%), and insulin ($n=4$, 5.5%). In contrast, all patients with type 1 diabetes who continued treatment were receiving insulin on admission.

The comparison of elderly and nonelderly patients with type 2 diabetes

Table 2 shows the clinical and laboratory findings associated with DKA among the elderly and nonelderly patients with type 2 diabetes. The elderly patients showed longer duration of diabetes, lower BMI, higher sodium levels, lower urinary C-peptide levels, and higher effective osmolality than the nonelderly patients with type 2 diabetes ($p<0.05$). No significant differences were observed in plasma glucose or HbA1c levels between the elderly and nonelderly patients. DKA onset under diabetes treatment occurred more frequently in elderly patients than in nonelderly patients (39.1% and 14.0%, respectively). However, only 1 elderly patient (4.3%) was newly diagnosed with diabetes, while 22 nonelderly patients (44.0%) were newly diagnosed with diabetes.

Table 1. Differences in the Clinical and Laboratory Findings of Diabetic Ketoacidosis between Patients with Type 2 and Type 1 Diabetes Mellitus.

	Patients with T2DM (n=73)	Patients with T1DM (n=85)	p value
Age (years)	55.8±18.9	45.2±17.2	<0.01*
Male, n (%)	53 (72.6)	48 (56.5)	0.046*
Duration of DM (years)	10 (3.0-15.5)	8.5 (2.3-15.0)	0.47
Consciousness disorder, n (%)	23 (31.5)	24 (28.2)	0.73
Abdominal symptoms, n (%)	26 (35.6)	45 (52.9)	0.04*
Abdominal pain, n (%)	4 (5.5)	12 (14.1)	0.11
Nausea or vomiting, n (%)	25 (34.2)	43 (50.6)	0.05
Diarrhea, n (%)	8 (11.0)	4 (4.7)	0.22
Hyperglycemic symptoms, n(%)	25 (34.2)	33 (38.8)	0.62
Symptoms' duration (days)	9.0 (5.0-23.0)	5.0 (2.0-8.3)	<0.01*
Abdominal symptoms (days)	10.0 (4.5-19.8)	3.0 (1.8-6.0)	<0.01*
Hyperglycemic symptoms (days)	16.0 (8.0-34.5)	7.0 (3.0-24.0)	0.03*
Infection, n (%)	23 (31.5)	16 (18.8)	0.10
Recurrent DKA, n (%)	13 (17.8)	20 (23.5)	0.44
Treatment status at the onset of DKA			
Untreated or self-interrupted DM treatment, n (%)	32 (43.8)	33 (38.8)	0.63
Under DM treatment, n (%)	16 (21.9)	20 (23.5)	0.85
SGLT2i user, n (%)	2 (2.7)	0 (0.0)	0.21
Insulin user, n (%)	4 (5.5)	20 (23.5)	<0.01
Newly diagnosed of DM, n(%)	23 (31.5)	32 (37.6)	0.50
BMI (kg/m ²)	23.4±5.7	21.6±3.8	0.03*
Plasma glucose (mg/dL)	677.8±271.5	772.8±337.9	0.06
HbA1c (%)	12.0±2.8	10.5±2.9	<0.01*
Serum C-peptide (ng/mL)	0.85 (0.5-1.8)	0.1 (0.1-0.2)	<0.01*
CPR index	0.5 (0.3-0.9)	0.06 (0.04-0.1)	<0.01*
SUIT index	14.3 (6.6-26.6)	1.6 (0.9-3.6)	<0.01*
Urinary C-peptide (μg/day)	30.7 (9.7-61.4)	3.7 (0.5-9.1)	<0.01*
eGFR (mL/min/1.73 m ²)	46.0 (25.0-75.0)	54.0 (31.8-80.0)	0.19
Sodium (mEq/L)	131.3±10.8	129.4±8.3	0.22
Potassium (mEq/L)	4.9±1.0	5.6±1.1	<0.01*
Chloride (mEq/L)	92.0±10.7	92.5±11.0	0.80
Total ketone bodies (mmol/L)	12.1±7.2	12.9±5.3	0.54
3β-hydroxybutyric acid (mmol/L)	9.3±5.5	9.9±4.2	0.56
pH	7.2±0.14	7.1±0.15	<0.01*
HCO ₃ ⁻ (mEq/L)	8.8 (3.5-14.2)	4.6 (2.7-7.8)	<0.01*

Data are presented as mean±standard deviation or median (interquartile range) or n (%). * Significant differences (p<0.05). T2DM: type 2 diabetes mellitus, T1DM: type 1 diabetes mellitus, DM: diabetes mellitus, SGLT2i: sodium-glucose cotransporter 2 inhibitors, DKA: diabetic ketoacidosis, BMI: body mass index, HbA1c: glycated hemoglobin, CPR index: serum C-peptide immunoreactivity index, SUIT index: secretory units of islets in transplantation index, eGFR: estimated glomerular filtration rate, HCO₃⁻: bicarbonate ion

The correlation between endogenous insulin secretion and other variables among type 2 diabetes cases

Table 3 shows the correlation between endogenous insulin secretion and other variables among patients with type 2 diabetes. Age had a significant negative correlation with the serum C-peptide levels, urinary C-peptide levels, and CPR index. The BMI had a significant positive correlation with the serum and urinary C-peptide levels. In addition, the serum C-peptide levels were significantly associated with the HCO₃⁻ levels and total ketone bodies.

Discussion

In the present study, we analyzed the clinical and laboratory data to identify parameters that might affect the onset and clinical course of DKA in Japanese patients by performing multiple comparisons. Our findings provide insight into the prevention and early detection of DKA.

The comparison of clinical features of DKA in patients with type 1 and type 2 diabetes

As expected, patients with type 2 diabetes were older than those with type 1 diabetes at the time of onset of DKA. Our

Table 2. Clinical and Laboratory Findings of Diabetic Ketoacidosis among Elderly (age ≥65) and Nonelderly (age <65) Patients with Type 2 Diabetes Mellitus.

	Elderly patients (n=23)	Nonelderly patients (n=50)	p value
Age (years)	74.0±9.5	47.4±10.1	<0.01*
Male, n (%)	10 (43.5)	43 (86.0)	<0.01*
Duration of DM (years)	15.0 (11.0-20.0)	5.0 (3.0-11.0)	0.01*
Consciousness disorder, n (%)	8 (34.8)	15 (30.0)	0.79
Abdominal symptoms, n (%)	5 (21.7)	21 (42.0)	0.12
Abdominal pain, n (%)	2 (8.7)	2 (4.0)	0.59
Nausea or vomiting, n (%)	5 (21.7)	20 (40.0)	0.19
Diarrhea, n (%)	1 (4.3)	7 (14.0)	0.42
Hyperglycemic symptoms, n (%)	8 (34.8)	17 (34.0)	1.00
Symptoms' duration (days)	7.5 (3.5-23.8)	10.0 (5.5-22.0)	0.60
Abdominal symptoms (days)	9.0 (8.0-10.0)	10.0 (4.0-21.0)	0.70
Hyperglycemic symptoms (days)	9.5 (7.5-10.8)	28.0 (10.0-39.0)	0.16
Infection, n (%)	9 (39.1)	14 (28.0)	0.42
Recurrent DKA, n (%)	2 (8.7)	11 (22.0)	0.21
Treatment status at the onset of DKA			
Untreated or self-interrupted DM treatment, n (%)	12 (52.1)	20 (40.0)	0.45
Under DM treatment, n (%)	9 (39.1)	7 (14.0)	0.03*
SGLT2i user, n (%)	0 (0.0)	2 (4.0)	0.21
Insulin user, n (%)	3 (13.0)	1 (2.0)	0.09
Newly diagnosed of DM, n (%)	1 (4.3)	22 (44.0)	<0.01*
BMI (kg/m ²)	19.1±3.1	25.4±5.6	<0.01*
Plasma glucose (mg/dL)	687.5±292.8	673.4±264.1	0.84
HbA1c (%)	12.0±2.7	11.9±2.8	0.82
Serum C-peptide (ng/mL)	0.6 (0.4-1.6)	0.9 (0.7-1.9)	0.13
CPR index	0.4 (0.2-0.7)	0.5 (0.4-0.9)	0.07
SUIT index	11.3 (5.1-22.9)	15.1 (6.9-27.7)	0.26
Urinary C-peptide (μg/day)	16.7 (5.8-46.2)	33.7 (19.0-65.5)	0.04*
eGFR (mL/min/1.73 m ²)	43.0 (22.0-54.0)	47.5 (26.8-82.8)	0.26
Sodium (mEq/L)	136.7±9.0	128.7±10.7	<0.01*
Potassium (mEq/L)	4.7±1.2	5.0±0.9	0.31
Total ketone bodies (mmol/L)	13.2±7.3	11.6±7.2	0.53
3β-hydroxybutyric acid (mmol/L)	10.9±5.1	8.6±5.7	0.23
pH	7.2±0.1	7.2±0.2	0.14
HCO ₃ ⁻ (mEq/L)	9.6 (7.5-15.7)	6.5 (3.3-12.6)	0.15
Effective osmolality (mOsm/L)	311.6±26.0	294.9±24.7	0.01*

Data are presented as mean±standard deviation or median (interquartile range) or n (%). * Significant differences (p<0.05). DM: diabetes mellitus, SGLT2i: sodium-glucose cotransporter 2 inhibitors, DKA: diabetic ketoacidosis, BMI: body mass index, HbA1c: glycated hemoglobin, CPR index: serum C-peptide immunoreactivity index, SUIT index: secretory units of islets in transplantation index, eGFR: estimated glomerular filtration rate, HCO₃⁻: bicarbonate ion

findings revealed that patients with DKA and type 2 diabetes showed less frequent abdominal symptoms and had a longer duration of symptoms than those with type 1 diabetes. A previous study reported that approximately 50% of patients with moderate-to-severe DKA developed abdominal pain, and the duration of abdominal pain, nausea, vomiting, and diarrhea was approximately 3 days (10). However, the difference in the frequency and duration of abdominal symptoms for each type of diabetes is unknown. Our study revealed that patients with DKA who had type 2 diabetes showed less-frequent abdominal symptoms that developed more slowly than among those with type 1 diabetes. These differences may be explained in part by the relatively high endogenous insulin secretion, pH values, and HCO₃⁻ levels

observed in patients with DKA with type 2 diabetes.

Clinical characteristics of DKA in nonelderly patients with type 2 diabetes

In the present study, only 14% of nonelderly patients with type 2 diabetes received diabetes treatment at the onset of DKA. A previous study reported that among young adult Japanese patients with type 2 diabetes, 49.4% of men and 35.7% of women were diagnosed with diabetes during their medical examination (21). In addition, the percentage of type 2 diabetes patients currently receiving treatment is 76.6% in Japan but just 51.5% among men in their 40s (22). Therefore, our findings suggest that neglecting proper treatment for diabetes is a major risk factor for developing DKA

Table 3. Correlation between Endogenous Insulin Secretion and Other Variables among Patients with Type 2 Diabetes Mellitus.

	Serum C-peptide		Urinary C-peptide		CPR index	
	r value	p value	r value	p value	r value	p value
Age (years)	-0.292	0.03*	-0.38	<0.01*	-0.316	0.02*
Duration of DM (years)	-0.322	0.06	-0.444	<0.01*	-0.129	0.47
Symptoms' duration (days)	0.412	<0.01*	0.102	0.47	0.226	0.13
BMI (kg/m ²)	0.400	<0.01*	0.41	<0.01*	0.21	0.16
Plasma glucose (mg/dL)	-0.088	0.53	0.076	0.58	-0.031	0.83
eGFR (mL/min/1.73 m ²)	-0.052	0.72	0.122	0.37	-0.086	0.55
Total ketone bodies (mmol/L)	-0.414	0.02*	-0.024	0.90	-0.355	0.047*
HCO ₃ ⁻ (mEq/L)	0.394	<0.01*	0.188	0.16	0.118	0.4
pH	0.242	0.08	0.042	0.76	0.051	0.72

* Significant differences (p<0.05). CPR index: serum C-peptide immunoreactivity index, DM: diabetes mellitus, BMI: body mass index, eGFR: estimated glomerular filtration rate, HCO₃⁻: bicarbonate ion

in young patients with type 2 diabetes. In fact, among 22 nonelderly patients who were newly diagnosed with type 2 diabetes, 13 had not undergone a medical examination in more than a year or were not receiving medical care even though an abnormal glucose tolerance had been pointed out to them (data not shown). Furthermore, the overconsumption of glucose-containing soft drinks can also lead to DKA (23). Chronic hyperglycemia induced by the excessive intake of soft drinks causes temporary beta-cell dysfunction and the loss of glucose-induced insulin secretion (24), resulting in a vicious circle of glucose toxicity and thirst, leading to ketosis. "Soft drink ketosis" that occurs in this way has been reported to be associated with a younger age, higher BMI, and greater insulin secretion capacity (25), which is consistent with the characteristics of the nonelderly patients with DKA in the present study. Providing appropriate information to patients is useful for preventing soft drink ketosis. Taken together, our findings suggest that improving the rate of medical examinations, follow-up examinations, and patient education are important for preventing the onset of DKA among nonelderly people with type 2 diabetes.

Clinical characteristics of DKA in elderly patients with type 2 diabetes

An increasing incidence of DKA in older patients has been reported recently (13). Older patients with DKA are associated with high mortality, and a large proportion of them have type 2 diabetes (13).

To our knowledge, the detailed clinical features of elderly Japanese patients with DKA have not been described. In the present study, a comparison between patients ≥65 years old and those <65 years old revealed the characteristics of elderly patients with DKA who had type 2 diabetes. First, the effective osmolality at the time of admission was significantly high, suggesting that more attention should be paid to the complications of hyperosmolality symptoms when treating elderly type 2 diabetes patients with DKA than younger ones. In addition, elderly patients with type 2 diabetes were characterized by a higher frequency of DKA onset under

diabetes treatment, lower BMI, longer duration of diabetes, and lower endogenous insulin secretion than younger ones, and most of these patients had no previous episodes of DKA. The aforementioned findings suggest that the age-related decline in insulin secretion, rather than insulin resistance, may be the trigger for the primary onset of DKA after a long treatment period. Thus, a lack of history of DKA along with long-term diabetes does not indicate a low risk for DKA development, even under poor glycemic control.

Recently, clinical inertia, defined as a delay in treatment intensification despite suboptimal glycemic control, was recognized as a risk factor for poor treatment outcomes (26). Our results imply that clinical inertia may also contribute to the development of DKA among lean and elderly patients with type 2 diabetes. The evaluation of changes in endogenous insulin secretion and the reconsideration of treatment should be considered essential during the long-term follow-up of patients with type 2 diabetes, particularly those with suboptimal glycemic control and/or weight loss.

Limitations and strength of the study

Several limitations associated with the present study warrant mention. First, the number of eligible patients was not large enough to evaluate the effect of different classes of antidiabetic agents on the onset of DKA. A previous study reported that diabetic patients using SGLT2is had a significantly increased risk of developing DKA (27) and needed longer treatment in the intensive-care unit than SGLT2is non-users (28). We were unable to evaluate the impact of SGLT2is in the present study because only two patients received SGLT2is among all participants. Second, we were unable to perform a multivariate analysis due to the small number of participants in this study, so hidden interactions might have influenced the results of our study. Third, parameters not considered in the current study might have affected the clinical characteristics of DKA. For example, although one study reported that a low socioeconomic status was strongly associated with DKA recurrence (29), our data lacked information on social background. Similarly, un-

known confounding factors might have affected our analyses. Fourth, although the variables for insulin secretory capacity were assessed after the completion of the initial treatment, significant hyperglycemia at the onset of DKA might have caused temporal glucose toxicity and affected the serum and urinary C-peptide levels. Finally, since this was a single-center observational study, the generalization of our findings may be limited. Nevertheless, the current study included a considerable number of elderly patients compared to previous reports (8, 15). The strength of the current study lies in its evaluation of the characteristics of DKA in an aging society.

Conclusion

This study provides helpful information on DKA prevention among patients with type 2 diabetes. Patients with type 2 diabetes who developed DKA showed a higher BMI and less frequent abdominal symptoms than those with type 1 diabetes. Elderly patients with type 2 diabetes who developed DKA were characterized by a high effective osmolality and low BMI. Furthermore, our findings imply that an age-related decline in the insulin secretory reserve after a long duration of type 2 diabetes may trigger the onset of DKA, sometimes even with ongoing diabetes treatment.

Author's disclosure of potential Conflicts of Interest (COI).

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