




Clinical profiles of hyperglycemic crises: A single-center retrospective study from Japan

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ABSTRACT

Aims/Introduction: The aim of the present study was to clarify the pathophysiologies of hyperglycemic crises in Japanese patients.

Materials and Methods: This was a retrospective study of patients with hyperglycemic crises admitted to Kumamoto Medical Center, Kumamoto, Japan, between 2012 and 2019. Patients were classified as having diabetic ketoacidosis (DKA), hyperglycemic hyperosmotic syndrome (HHS) or a mixed state of the two conditions (MIX), and laboratory data and levels of consciousness at hospital admission, as well as the rates of mortality and coagulation disorders, were compared.

Results: The diagnostic criteria for hyperglycemic crisis were met in 144 cases, comprising 87 (60.4%), 38 (26.4%) and 19 (13.2%) cases of DKA, HHS and MIX, respectively. Type 1 diabetes was noted in 46.0 and 26.3% of patients in the DKA and MIX groups, respectively. Fibrin degradation product and D-dimer levels were significantly higher in the HHS group than in the DKA group (DKA and HHS groups: fibrin degradation product 7.94 ± 8.43 and 35.54 ± 51.80 $\mu\text{g/mL}$, respectively, $P < 0.01$; D-dimer 2.830 ± 2.745 and 14.846 ± 21.430 $\mu\text{g/mL}$, respectively, $P < 0.01$). Mortality rates were 5.7, 13.2 and 5.3% in the DKA, HHS and MIX groups, respectively. Seven patients (4.9%), four of whom were in the MIX group, had acute arterial occlusive diseases.

Conclusions: The low frequency of type 1 diabetes in DKA and MIX might be responsible for reduced insulin secretion in Japanese populations. Patients with hyperglycemic crises have increased coagulability, and acute arterial occlusion needs to be considered, particularly in MIX.

INTRODUCTION

Hyperglycemic crises, such as diabetic ketoacidosis (DKA) and hyperglycemic hyperosmotic syndrome (HHS), are still highly life-threatening if treated incorrectly in the early stages; therefore, it is important to acquire sufficient knowledge, and practice accurate and prompt treatment.

As mortality among patients with hyperglycemic crises is related to age, the level of consciousness on admission, severity of acidosis and degree of hyperosmolarity¹, more detailed information is required on the pathophysiologies of hyperglycemic crises.

Racial differences have been reported in the pathophysiologies of diabetes. For example, the incidence of acute-onset type 1 diabetes in Japan is less than one-tenth that in the USA and Europe². Furthermore, insulin secretion capacities in patients with type 2 diabetes are lower in Japan than in the USA, whereas insulin sensitivity is higher in Japan than in the USA³. Even in hyperglycemic crises, soft drink ketoacidosis might be unique to Japanese patients^{4,5}. Although racial differences have been reported, limited information is currently available on the pathophysiologies of hyperglycemic crises in Japan. Therefore, the present study retrospectively analyzed the pathophysiologies of patients with hyperglycemic crises who were treated at Kumamoto Medical Center, Kumamoto, Japan, between 2012 and 2019.

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METHODS

Patients

The study protocol was approved by the institutional review board of Kumamoto Medical Center, Kumamoto, Japan.

We carried out a retrospective analysis of hospital admissions for hyperglycemic crises that included DKA, HHS and a mixed state of the two conditions (MIX) in patients admitted between 2012 and 2019. We used admission or discharge diagnoses (International Classification of Diseases, 10th Revision) to identify patients with hyperglycemic crises.

Hyperglycemic crises were diagnosed according to the diagnostic criteria of the American Diabetes Association⁶, the Japan Diabetes Society⁷ and the Joint British Diabetes Society⁸. DKA was defined as the presence of hyperglycemia (first glucose level >250 mg/dL), acidosis (arterial or venous pH \leq 7.30 and/or $\text{HCO}_3^- \leq$ 15 mEq/L) and ketonuria in the absence of elevated effective plasma osmolality (E_{OSM} ; \leq 320 mOsm/L). HHS was defined as the presence of hyperglycemia (first glucose level >600 mg/dL) and elevated E_{OSM} (>320 mOsm/L) in the absence of acidosis (arterial or venous pH >7.30 and $\text{HCO}_3^- >$ 15 mEq/L). MIX was defined as hyperglycemia (first glucose level >600 mg/dL), acidosis (arterial or venous pH \leq 7.30 and/or $\text{HCO}_3^- \leq$ 15 mEq/L), ketonuria and elevated E_{OSM} (>320 mOsm/L). Patients with disseminated cancer were excluded from the study group.

Data retrieval

Data were retrieved by a detailed analysis of hospital medical records. The following data were recorded for all patients: age, sex, height and weight, history of diabetes, type of diabetes diagnosed, treatment of diabetes before the onset of hyperglycemic crises, and precipitating causes of hyperglycemic crises. The following parameters were collected at hospital admission: consciousness level (Japan Coma Scale [JCS]), plasma glucose, glycated hemoglobin, Na, K, Cl, estimated glomerular filtration rate, results of a urine test strip analysis, pH, bicarbonate ion, lactate, C-reactive protein (CRP), procalcitonin, white blood cells, hemoglobin, platelet count, prothrombin time-international normalized ratio (PT-INR), fibrinogen, fibrin and fibrinogen degradation products (FDP), and D-dimer. To obtain information on eventual vascular complications of hyperglycemic crises, we collected data on the in-hospital occurrence of acute arterial occlusive diseases (stroke, acute coronary syndrome, acute abdominal or peripheral thrombosis and acute mesenteric ischemia) and venous thrombosis (deep vein thrombosis and pulmonary thromboembolism). Outcomes and the most likely cause of death were recorded.

Statistical analysis

Results are presented as the mean \pm standard deviation for continuous variables, and as absolutes (number) and relative frequencies (percentage) for categorical variables. An unpaired *t*-test or analysis of variance followed by the Bonferroni test were used to compare continuous variables. The Kruskal–Wallis

test followed by the Mann–Whitney *U*-test with the Bonferroni test were used to compare ordinal variables. Fisher's exact test followed by a residual analysis was used to compare categorical variables. A logistic regression analysis was carried out with death as the dependent variable. All analyses were carried out using SPSS 14.0-J (SPSS Japan, Ibaraki, Japan), and a *P*-value <0.05 (two-tailed) was considered to be significant.

RESULTS

Patient characteristics

In total, 144 patients met the diagnostic criteria of hyperglycemic crises and were divided into three groups – DKA, HHS and MIX – with 87 (60.4%), 38 (26.4%) and 19 (13.2%) patients, respectively. Patients with DKA were significantly younger (Table 1). Type 1 diabetes was only detected in patients with DKA and MIX. Type 2 diabetes was observed in all groups, and was particularly prevalent in patients with HHS. Although the rate of type 2 diabetes was significantly lower in patients with DKA, it was still present in 39.1% of patients. Among patients with secondary diabetes, nine with DKA and one with MIX had pancreatic diabetes.

Drug treatments for diabetes before the onset of hyperglycemic crises were not received by 35.6, 57.9 and 47.4% of patients in the DKA, HHS and MIX groups, respectively, with a significantly higher rate in the HHS group and significantly lower rate in the DKA group. Details on oral medications are shown in Table S1. Insulin treatments were significantly more frequent in the DKA group. Although self-reported, there was no previous diagnosis of diabetes in 29.9, 31.6 and 42.1% of patients in the DKA, HHS and MIX groups, respectively. Medication, mainly insulin treatment interruptions, was discontinued in 49.4, 15.8 and 42.1% of patients in the DKA, HHS and MIX groups, respectively, with a significantly higher rate in the DKA group and significantly lower rate in the HHS group. The complication of infection was noted in many cases (Table S2 for details). The overconsumption of sugar-containing soft drinks was noted in 24.1, 7.9 and 47.4% of patients in the DKA, HHS and MIX groups, respectively, with a significantly higher result in the MIX group. When soft drink ketoacidosis was defined as a case of type 2 diabetes mellitus in which the overconsumption of sugar-containing soft drinks was considered to have led to the development of DKA or MIX, patients with soft drink ketoacidosis were significantly younger and had a higher BMI than those without the overconsumption of sugar-containing soft drinks in both the DKA and MIX groups (Tables S3,S4).

Level of consciousness

The levels of consciousness of patients at the time of their visit were assessed by the JCS. The Glasgow Coma Scale is the international gold standard for level of consciousness assessments, whereas JCS is widely used by Japanese clinical facilities. The JCS is based on arousal degrees and categorized into three stages: grade 1, aroused; grade 2, aroused in response to

Table 1 | Characteristics of patients with hyperglycemic crises

	DKA (n)		HHS (n)		MIX (n)		P-value
Age (years)	49.4 ± 19.7	(87)	74.6 ± 14.9**	(38)	64.9 ± 21.1**	(19)	<0.001
BMI	22.7 ± 6.2	(85)	20.4 ± 4.6	(35)	21.9 ± 5.2	(19)	0.148
Male, n (%)	47 (54.0)	(87)	20 (52.6)	(38)	16 (84.2) [§]	(19)	0.037
Type of diabetes mellitus							
Type 1, n (%)	40 (46.0) [¶]	(87)	0 (0.0) [‡]	(38)	5 (26.3)	(19)	<0.001
Type 2, n (%)	34 (39.1) [‡]	(87)	36 (94.7) [¶]	(38)	13 (68.4)	(19)	
Secondary, n (%)	10 (11.5)	(87)	1 (2.6)	(38)	1 (5.3)	(19)	
Unknown, n (%)	3 (3.4)	(87)	1 (2.6)	(38)	0 (0.0)	(19)	
Treatment of diabetes mellitus before the onset of hyperglycemic crises							
No medication, n (%)	31 (35.6) [†]	(87)	22 (57.9) [§]	(38)	9 (47.4)	(19)	0.004
Oral antidiabetic drugs only, n (%)	15 (17.2)	(87)	11 (28.9)	(38)	5 (26.3)	(19)	
Insulin only, n (%)	36 (41.4) [¶]	(87)	3 (7.9) [‡]	(38)	3 (15.8)	(19)	
GLP-1 only, n (%)	0 (0.0)	(87)	0 (0.0)	(38)	0 (0.0)	(19)	
Insulin with oral antidiabetic drugs, n (%)	4 (4.6)	(87)	2 (5.3)	(38)	2 (10.5)	(19)	
GLP-1 with oral antidiabetic drugs, n (%)	0 (0.0)	(87)	0 (0.0)	(38)	0 (0.0)	(19)	
Insulin with GLP-1, n (%)	0 (0.0)	(87)	0 (0.0)	(38)	0 (0.0)	(19)	
Insulin with GLP-1 and oral antidiabetic drugs, n (%)	1 (1.1)	(87)	0 (0.0)	(38)	0 (0.0)	(19)	
Precipitating causes (with multiple selections)							
Newly diagnosed diabetes mellitus, n (%)	26 (29.9)	(87)	12 (31.6)	(38)	8 (42.1)	(19)	0.598
Discontinuation of medications, n (%)	43 (49.4) [¶]	(87)	6 (15.8) ^f	(38)	8 (42.1)	(19)	0.001
Infection, n (%)	43 (49.4)	(87)	26 (68.4)	(38)	11 (57.9)	(19)	0.136
Overconsumption of sugar-containing soft drinks, n (%)	21 (24.1)	(87)	3 (7.9) [‡]	(38)	9 (47.4) [¶]	(19)	0.003

Data are the mean ± standard deviation, (n). ***P* < 0.01 versus DKA. †Adjusted standardized residual <−1.96 (significance level *P* = 0.05). ‡Adjusted standardized residual <−2.58 (significance level *P* = 0.01). §Adjusted standardized residual >1.96 (significance level *P* = 0.05). ¶Adjusted standardized residual >2.58 (significance level *P* = 0.01). BMI, body mass index; GLP-1, glucagon-like peptide-1; MIX, mixed diabetic ketoacidosis/hyperglycemic hyperosmolar state.

stimuli; and grade 3, not aroused, even when stimulated. Grade 0 is considered to be clear consciousness. A correlation was previously reported between JCS and Glasgow Coma Scale assessments⁹.

Grade 0 was significantly more frequent in the DKA group (Table 2). In contrast, grade 2 was significantly more frequent in the MIX group, and grade 3 in the HHS group. Therefore, the level of consciousness at the onset of hyperglycemic crises was mild in the DKA group, and severe in the HHS and MIX groups.

Laboratory data

Plasma glucose levels significantly differed between groups in the order of MIX > HHS > DKA (Table 3). Blood glucose levels in the MIX group were >1,000 mg/dL. Glycated hemoglobin was also the highest in the MIX group and significantly higher than in the HHS group. Serum Na levels were high in the HHS group, but normal in the MIX group and pseudohyponatremia in the DKA group. Serum K levels were significantly higher in the DKA group than in the HHS group. The HHS and MIX groups had significantly lower estimated

Table 2 | Levels of consciousness in patients with hyperglycemic crises

	DKA (n = 87)	HHS (n = 38)	MIX (n = 19)	P-value
JCS grade 0, n (%)	40 (46.0) [¶]	1 (2.6) [‡]	1 (5.3) [†]	<0.001
JCS grade 1, n (%)	27 (31.0)	16 (42.1)	6 (31.6)	
JCS grade 2, n (%)	12 (13.8) [†]	9 (23.7)	8 (42.1) [¶]	
JCS grade 3, n (%)	8 (9.2) [‡]	12 (31.6) [¶]	4 (21.1)	

†Adjusted standardized residual <−1.96 (significance level *P* = 0.05). ‡Adjusted standardized residual <−2.58 (significance level *P* = 0.01). ¶Adjusted standardized residual > 2.58 (significance level *P* = 0.01). DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; JCS, Japan Coma Scale; JCS grade 0, alert; JCS grade 1, possible eye-opening, not lucid; JCS grade 2, possible eye-opening upon stimulation; JCS grade 3, no eye-opening and coma; MIX, mixed diabetic ketoacidosis/hyperglycemic hyperosmolar state.

Table 3 | Laboratory data of patients with hyperglycemic crises

	DKA (n)	HHS (n)	MIX (n)	P-value	Reference range
Glucose (mg/dL)	660.1 ± 274.4 (87)	911.0 ± 258.0 [‡] (38)	1175.2 ± 400.2 ^{‡,¶} (19)	<0.001	70–109
HbA1c (%)	11.22 ± 3.14 (86)	9.62 ± 2.19 [†] (36)	12.16 ± 3.36 [§] (18)	0.005	4.9–6.0
Effective osmolarity (mOsm/L)	294.4 ± 13.4 (87)	357.0 ± 25.8 [‡] (38)	342.9 ± 19.2 ^{‡,§} (19)	<0.001	
Na (mEq/L)	128.9 ± 7.5 (87)	153.2 ± 13.3 [‡] (38)	138.8 ± 10.7 ^{‡,¶} (19)	<0.001	138–145
K (mEq/L)	5.09 ± 1.19 (87)	4.36 ± 0.82 [‡] (38)	5.05 ± 1.16 (19)	0.003	3.6–4.8
Cl (mEq/L)	93.8 ± 9.6 (87)	112.8 ± 12.2 [‡] (38)	97.5 ± 12.4 [¶] (19)	<0.001	101–108
eGFR	63.74 ± 54.35 (84)	31.32 ± 17.59 [‡] (38)	23.76 ± 12.98 [‡] (19)	<0.001	60.0–
Ketone bodies in urine	2.97 ± 1.22 (86)	0.39 ± 0.74 [‡] (38)	1.53 ± 1.15 ^{‡,¶} (19)	<0.001	
Total ketone bodies in blood (µmol/L)	12181.8 ± 4860.3 (44)		11342.8 ± 5736.8 (11)	0.623	0–130
pH	7.113 ± 0.168 (87)	7.395 ± 0.074 [‡] (37)	7.113 ± 0.159 [¶] (19)	<0.001	7.35–7.45
Bicarbonate ion (mmol/L)	7.43 ± 4.76 (84)	26.61 ± 7.94 [‡] (37)	9.57 ± 5.60 [¶] (18)	<0.001	23–28
Lactate (mmol/L)	3.09 ± 2.36 (87)	3.23 ± 1.76 (37)	4.77 ± 3.45 [†] (19)	0.023	
CRP (mg/dL)	6.782 ± 11.753 (84)	3.850 ± 4.783 (37)	4.453 ± 5.654 (18)	0.265	0.00–0.14
PCT (ng/mL)	3.431 ± 7.484 (36)	0.759 ± 0.895 (18)	7.444 ± 10.336 (8)	0.073	0.00–0.50
WBC (µL)	16724.6 ± 8947.6 (87)	13635.8 ± 7116.6 (38)	17204.2 ± 5547.0 (19)	0.119	3300–8600
Hb (g/dL)	13.94 ± 2.62 (87)	14.37 ± 2.83 (38)	15.19 ± 2.36 (19)	0.166	13.7–16.8
PLT (×10 ⁴ /µL)	24.56 ± 9.28 (86)	22.12 ± 8.12 (38)	24.66 ± 11.05 (19)	0.374	15.8–34.8
PT-INR	1.114 ± 0.165 (77)	1.309 ± 0.602 [†] (36)	1.101 ± 0.080 (19)	0.014	0.85–1.15
Fibrinogen (mg/dL)	400.2 ± 196.3 (35)	398.6 ± 115.3 (17)	363.0 ± 137.1 (12)	0.794	200–400
FDP (µg/mL)	7.94 ± 8.43 (38)	35.54 ± 51.80 [‡] (24)	17.61 ± 31.49 (14)	0.007	0.0–5.0
D-dimer (µg/mL)	2.830 ± 2.745 (38)	14.846 ± 21.430 [‡] (22)	6.230 ± 10.669 (13)	0.003	0.00–1.00

Data are the mean ± standard deviation. [†]*P* < 0.05 versus diabetic ketoacidosis (DKA). [‡]*P* < 0.01 versus DKA. [§]*P* < 0.05 versus hyperglycemic hyperosmolar state (HHS). [¶]*P* < 0.01 versus HHS. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FDP, fibrin and fibrinogen degradation products; Hb, hemoglobin; HbA1c, glycated hemoglobin; MIX, mixed diabetic ketoacidosis/hyperglycemic hyperosmolar state; PCT, procalcitonin; PLT, platelets; PT-INR, prothrombin time-international normalized ratio; WBC, white blood cells.

glomerular filtration rates than the DKA group, suggesting the presence of strong dehydration. The majority of patients in the HHS and MIX groups had elevated estimated glomerular filtration rates after the normalization of blood glucose (Table S5). Urine ketone levels significantly differed between groups in the order of DKA > MIX > HHS; however, total ketone bodies in blood did not significantly differ in the DKA and MIX groups. Blood ketones were rarely measured in the HHS group. CRP, procalcitonin and white blood cells were elevated in all groups, but did not significantly differ between groups. PT-INR was also slightly prolonged in all groups, and was significantly longer in the HHS group than in the DKA group. FDP and D-dimer levels were elevated in all groups, and were significantly higher in the HHS group than in the DKA group, and slightly higher in the MIX group than in the DKA group.

Rates of mortality and coagulation disorders

Mortality rates were 5.7, 13.2 and 5.3% in the DKA, HHS and MIX groups, respectively (Table 4), with no significant differences between groups. The causes of death were as follows: two cases of sepsis, two of DIC and one of acute renal failure in the DKA group; two of sepsis, one of DIC, one of malignant syndrome and one unknown cause of death in the HHS group; and complications of acute arterial occlusion in all cases in the MIX group.

To identify predictors of a poor prognosis, all cases of hyperglycemic crises were divided into survival and death groups, and factors were compared (Tables S6,S7). Na, Cl and PT-INR levels were significantly higher, whereas CRP levels were slightly higher in the death group than in the survival group. In addition to the previously examined parameters of age, the level of

Table 4 | Rates of mortality and arterial or vein diseases in patients with hyperglycemic crises

	DKA (n = 87)	HHS (n = 38)	MIX (n = 19)	P-value
Dead, n (%)	5 (5.7)	5 (13.2)	1 (5.3)	0.320
Acute arterial occlusive disease, n (%)	0 (0.0) [‡]	3 (7.9)	4 (21.1) [¶]	<0.001
Venous thrombosis, n (%)	1 (1.1)	2 (5.3)	2 (10.5)	0.059

[‡]Adjusted standardized residual <−2.58 (significance level *P* = 0.01). [¶]Adjusted standardized residual >2.58 (significance level *P* = 0.01). DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; MIX, mixed diabetic ketoacidosis/hyperglycemic hyperosmolar state.

Table 5 | Logistic regression analysis with selected independent variables

	B	Standard error	P-value	Odds ratio (95% CI)
Age (years)	-0.007	0.024	0.752	0.993 (0.948–1.040)
JCS grade	-0.811	0.570	0.155	0.445 (0.145–1.359)
pH	-3.457	2.934	0.239	0.032 (0.000–9.901)
Effective osmolality (mOsm/L)	-0.003	0.028	0.911	0.997 (0.943–1.054)
Na (mEq/L)	0.079	0.070	0.256	1.082 (0.944–1.241)
PT-INR	4.910	1.738	0.005	135.705 (4.498–4094.003)
CRP (mg/dL)	0.063	0.032	0.046	1.066 (1.001–1.134)

CI, confidence interval; CRP, C-reactive protein; JCS, Japan Coma Scale; PT-INR, prothrombin time-international normalized ratio.

consciousness, pH, and osmolality, Na, CRP and PT-INR in the present study were added as independent variables, and a logistic regression analysis was carried out (Table 5). PT-INR and CRP were identified as independent risk factors. The addition of warfarin as an independent factor did not change the results of the analysis. Coagulation abnormalities and infections might be involved in the cause of death in hyperglycemic crises; however, due to the small number of cases, further studies are required.

Seven out of 144 patients (4.9%) had acute arterial occlusive diseases, including three cases of cerebral infarctions, two of non-obstructive mesenteric ischemia and two of acute arterial occlusion of the lower extremities. Cerebral infarction was associated with HHS, and all other acute arterial occlusive diseases were associated with MIX. The incidence of acute arterial occlusive diseases was significantly higher in the MIX group. The clinical profiles of patients with acute arterial occlusive diseases and the rates of comorbidities associated with atherosclerosis are shown in Tables S8–S10, respectively. The rates of hypertension, previous cerebral infarction and previous myocardial infarction were significantly higher in the HHS group. Two of the three patients in the HHS group with cerebral infarction also had previous cerebral infarction. In contrast, four patients in the MIX group with non-obstructive mesenteric ischemia or acute arterial occlusion of the lower extremities had no atherosclerosis-related comorbidities.

DISCUSSION

In the present study, hyperglycemic crises were divided into three groups: DKA, HHS and MIX. DKA and HHS were diagnosed according to the diagnostic criteria of the American Diabetes Association⁶ and Japan Diabetes Society⁷. Acidosis was measured by venous blood gas in some cases, and, thus, was diagnosed using the diagnostic criteria of the Joint British Diabetes Society⁸. The Joint British Diabetes Society recommends the use of venous blood gas, which is safer than arterial blood gas, to diagnose acidosis, and reported the similar diagnostic power of venous and arterial blood gas. Therefore, they advocate the use of venous blood gas for the diagnosis of DKA in emergency medical care in which the rapid diagnosis of hyperglycemic crises is required⁸. The concept of using venous blood

gas for the diagnosis of DKA needs to be examined in further studies.

HHS and DKA are not incompatible with each other, and are both caused by insufficient insulin levels¹. They often occur simultaneously, and one-third of patients with hyperglycemic crises show characteristics of both HHS and DKA¹. However, the American Diabetes Association and Japan Diabetes Society guidelines do not include diagnostic criteria for this mixed condition. Therefore, in the present study, MIX was defined as hyperglycemia (first glucose level >600 mg/dL), acidosis (arterial or venous pH \leq 7.30 and/or $\text{HCO}_3^- \leq$ 15 mEq/L), ketonuria and elevated E_{OSM} (>320 mOsm/L).

A previous study carried out in Rhode Island, USA ($n = 525$), reported DKA, HHS and MIX in 19.6, 55.4 and 25.0%, respectively, of the patients examined¹⁰, which is in contrast to the present results. A study carried out in Melbourne, Australia ($n = 312$), detected DKA, HHS and MIX in 54.8, 15.1 and 30.1%, respectively, of the patients analyzed¹¹, which is consistent with the present results; however, the percentage of MIX was higher. In 2004, a study carried out in Aichi Prefecture, Japan, reported DKA and HHS in 58.3 and 41.7% ($n = 72$), respectively, of patients¹². In the present study, when MIX was included in DKA results, 73.6 and 26.4% of patients had DKA and HHS, respectively. The percentage of HHS was higher in the Aichi study than in the present results. These differences might be due in part to the influences of racial differences and the environment due to regional characteristics. In addition, the Rhode Island study defined the hyperosmolality of HHS as plasma osmolality > 320 mOsm/L or $E_{\text{OSM}} > 310$ mOsm/L¹⁰, whereas the Melbourne study defined hyperosmolality in the HHS group as plasma osmolality >330 mOsm/L¹¹. The Melbourne study reported similar hyperosmolality in HHS to the present results, but lower than that in the Rhode Island study. The Aichi study was in the form of a questionnaire, and the diagnosis was left to the judgment of the physician in charge¹². Thus, variations in diagnostic criteria might have contributed to the differences observed in frequency.

The relationship between the development of DKA and type of diabetes is considered to vary with race. Balasubramanyam *et al.*¹³ reported that 80% of white patients who developed DKA had type 1 diabetes, whereas 53 and 34% of African

American and Hispanic patients, respectively, had type 1 diabetes. In addition, Newton *et al.*¹⁴ found that 87.5, 73.8 and 81.3% of white, African American and Hispanic patients, respectively, who developed DKA had type 1 diabetes. However, 38.1 and 46.0% of patients with type 1 diabetes in the Aichi study¹² and the present study, respectively, developed DKA, and the frequency of type 1 diabetes was lower than that in white patients. The frequency of type 1 diabetes was even lower in the MIX group, which showed ketoacidosis, as well as DKA. There are several possible reasons for this phenomenon. Japanese patients with type 2 diabetes have a low insulin secretion capacity¹⁵. Therefore, the additional reduction in insulin secretion due to glucotoxicity might easily result in DKA. Furthermore, although limited information is currently available from other countries, ketoacidosis has been reported in Japanese patients with type 2 diabetes due to the overconsumption of sugar-containing soft drinks^{4,5}. In the present study, soft drink ketoacidosis was suspected in 14.9 and 47.4% of patients with DKA and MIX, respectively (Tables S3,S4). Soft drink ketoacidosis in Japanese patients might partly explain the low frequency of type 1 diabetes in the DKA group. Furthermore, the present study showed that 10.3% of patients in the DKA group had secondary diabetes as a result of postoperative pancreatic cancer or chronic pancreatitis (i.e., pancreatic diabetes). The high frequency of pancreatic diabetes, which is considered to be low in the USA and Western European countries¹⁶, might also have contributed to the relatively low frequency of type 1 diabetes in the DKA group in the present study.

Abnormalities in the coagulation system have been reported to occur in hyperglycemic crises at a higher frequency in the HHS group than in the DKA group^{1,17–19}. Consistent with these findings, FDP and D-dimer levels in the present study were higher than the normal range in all groups; they were significantly higher in the HHS group than in the DKA group. In the MIX group, FDP and D-dimer levels were lower than in the HHS group and higher than in the DKA group. As serum Na levels and E_{OSM} were significantly higher in the HHS group than in the MIX and DKA groups, and hypernatremia and marked dehydration suggested by hypernatremia have been reported to alter an increased coagulation capacity^{19,20}, hypernatremia in the HHS group might have affected high FDP and D-dimer levels. There were seven cases of acute arterial occlusive diseases in the present study, with a significantly higher frequency in the MIX group. Although epidemiological data on the relationship between hyperglycemic crises and acute arterial occlusive disease are limited, Megarbane *et al.*²¹ found that four out of 17 patients with HHS admitted to the intensive care unit had the complication of limb ischemia. There are also scattered case reports of acute arterial occlusive diseases complicated by DKA^{22,23}; however, some of the reported cases were MIX in our classification^{24–26}. MIX might be the strongest risk factor for acute arterial occlusive diseases among all hyperglycemic crises, and, thus, further large-scale studies are warranted.

In the present study, mortality rates were 5.7, 13.2 and 5.3% in the DKA, HHS and MIX groups, respectively. The mortality rate of DKA ranged between 1 and 40%, depending on the region^{6,27–32}. Due to the high mortality rate in developing countries, the impact of the medical environment appears to be significant. In contrast, the mortality rate might be higher in the elderly and patients with severe comorbid conditions^{33,34}. Mortality rates in the present study were similar to or slightly higher than those in developed countries. This might have been influenced by the present study being a single-center study and our hospital being a tertiary care center. The mortality rate was previously shown to be markedly higher for HHS than for DKA at 10–20.0%^{19,35}, which was consistent with our results. In the present study, the rates of infectious complications in the DKA, HHS and MIX groups were as high as 49.4, 68.4 and 57.9%, respectively, and sepsis was the cause of death in four out of 11 patients (36.3%). A previous study reported that 30% of deaths in DKA patients in Denmark were due to infection²⁹. Infection is not only an incentive for the development of hyperglycemic crises, but might also be a cause of death in hyperglycemic crises patients. In the present study, death due to coagulation abnormalities, such as disseminated intravascular coagulation and acute arterial occlusive disease, occurred in as many as four out of 11 patients (36.3%). The mean levels for FDP and D-dimer, coagulation markers, were also high in all groups. As the complication of embolism in hyperglycemic crises has been reported to increase the mortality rate³⁶, the monitoring of coagulation disorders with appropriate tests, such as measurements of coagulation markers and vascular echocardiography, is important for reducing the mortality rate of hyperglycemic crises.

The potential limitations of the present study need to be considered. This was a single cohort study and, thus, does not represent the entire population of patients with hyperglycemic crises in Japan. Our hospital is a tertiary care center, and might have a high percentage of critically ill patients. As the factors indicated in the analysis of precipitating causes relied on questioning from patients or their family members and the diagnosis of the type of diabetes was extracted from the medical records of doctors, accuracy might have been affected. Furthermore, this was a retrospective study; therefore, omissions of measurements, such as coagulation markers, were evident. Additionally, venous thrombosis might not be diagnosed without a proper examination, such as by ultrasonography, and, thus, the potential for venous thrombosis might have been more prevalent. Although data were obtained from a single center, few studies have been carried out on the pathophysiology of hyperglycemic crises in Japan. Therefore, we consider the present study to provide novel insights into the pathophysiology of hyperglycemic crises in Japan.

In conclusion, we carried out a retrospective analysis of patients with hyperglycemic crises who were treated at our hospital between 2012 and 2019, and the following results were obtained. First, type 1 diabetes was less common in Japanese patients with DKA and MIX. We hypothesized that this might

have been due to the pathophysiologies of impaired insulin secretion in the Japanese population. Second, patients with HHS and MIX showed increased coagulability, and MIX patients had a significantly higher incidence of acute arterial occlusive diseases than those with DKA and HHS. Third, mortality rates were higher in HHS patients than in DKA and MIX patients, and sepsis and coagulation disorders were the most common causes of death. The management of infections and coagulation disorders, particularly acute arterial occlusion in the MIX group, needs to be considered when treating hyperglycemic crises.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Details of oral medications for patients with hyperglycemic crises.

Table S2 | The origin of infections in patients with hyperglycemic crises (with multiple selections).

Table S3 | Characteristics of patients with soft drink ketoacidosis.

Table S4 | Laboratory data of patients with soft drink ketoacidosis.

Table S5 | Laboratory data at onset and post-treatment of patients with hyperglycemic crises.

Table S6 | Characteristics of patients with hyperglycemic crises in survival and death groups.

Table S7 | Laboratory data of patients with hyperglycemic crises in survival and death groups.

Table S8 | Characteristics of patients with acute arterial occlusive diseases.

Table S9 | Laboratory data of patients with acute arterial occlusive diseases.

Table S10 | Rate of comorbidities associated with atherosclerosis in patients with hyperglycemic crises.