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ORIGINAL RESEARCH

Relationship Between Bedside Ketone Levels and Time to Resolution of Diabetic Ketoacidosis: A Retrospective Cohort Study

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ABSTRACT

Introduction: There is no information on the factors that influence the time required to induce resolution of diabetic ketoacidosis (DKA). New methods are currently available for bedside measurement of serum 3-hydroxybutyrate (3HB). The aim of this study was to determine the relationship between serum 3HB and the time to DKA resolution.

Methods: We reviewed the medical records of patients with type 1 diabetes (T1D) and a history of DKA who were admitted to the Department of Pediatrics, Osaka City University Hospital, between November 2008 and October 2018. DKA resolution was defined as 3HB below 1.0 mmol/L as measured by a bedside ketone meter.

Results: Data of 52 T1D-DKA episodes were analyzed (median age, 8.0 years; 20 male patients; 32 female patients; new T1D diagnosis, $n = 13$; established diagnosis, $n = 39$). In all cases, correction of serum 3HB was an important aspect of T1D management. The median time to DKA resolution (defined as the time from the start of insulin infusion until the fall of 3HB level to below 1.0 mmol/L) was 11 and 10 h in new and established T1D cases, respectively. 3HB on admission and the required insulin infusion dose per body weight, but not blood pH level on admission, correlated with time to DKA resolution. There was no relationship between blood pH level and 3HB on admission.

Conclusions: Our results showed that DKA resolution could be achieved within 10–11 h when DKA treatment is guided by bedside 3HB monitoring without any severe complications. Blood 3HB level is a potentially suitable marker for the severity and resolution of DKA.

Keywords: Bedside ketone body monitoring; Diabetic ketoacidosis; Insulin dose; Time to ketoacidosis resolution; Type 1 diabetes

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Key Summary Points

Why carry out this study?

To determine the relationship between bedside measurement of serum 3-hydroxybutyrate (3HB) and time to resolution of diabetic ketoacidosis (DKA) in patients with type 1 diabetes (T1D) in Japan.

What was learned from this study?

In newly diagnosed patients with T1D, bedside 3HB on admission, but not blood pH, correlates significantly with the time to resolution of DKA.

The insulin dose required for DKA resolution was less than 2.0 units per kilogram body weight.

INTRODUCTION

Diabetic ketoacidosis (DKA) is caused by relative or absolute insulin deficiency and is characterized clinically by hyperglycemia, metabolic acidosis, and ketonemia [1]. DKA is frequently encountered in daily clinical practice, in both newly diagnosed cases (up to 70%) and patients with established type 1 diabetes (T1D) (rate, 1–10% per case per year) [2]. The common risk factors for DKA include new diagnosis of T1D, young children, adolescent female patients, delayed T1D diagnosis, insulin omission, poor treatment on a sick day, accessibility to hospitals, and insulin pump injection errors [2–7].

DKA is one of the most severe and sometimes life-threatening acute complications; therefore, establishing a standard treatment protocol is needed to prevent further complications [8]. There are currently only a few established treatment regimens for DKA treatment. For example, the International Society for Pediatric and Adolescent Diabetes released recently consensus guidelines for DKA [2]; however, the guidelines cited only a few solid evidence-based treatment protocols for pediatric patients [9, 10]. Surprisingly, the time to DKA resolution (time between the start of treatment and resolution of DKA) remains ill-defined. DKA resolution is generally judged comprehensively on the basis of clinical signs, such as the ability to eat/drink and/or a few non-specific biomarkers, such as the blood pH value [2, 11]. Of these biomarkers, the Joint British Diabetes Societies recommended using bedside measurement of serum 3-hydroxybutyrate (3HB) to monitor the response to DKA treatment [11]. In this regard, bedside 3HB has been reported to correlate well with blood pH levels [12–16], as well as with plasma ketone [17–19]. On the basis of this, a number of studies investigated the usefulness of bedside ketone body monitoring to the response to treatment of DKA [13, 17, 20–23].

We have experienced numerous cases of acute DKA that were managed clinically at our hospital, including bedside ketone body measurement. To our knowledge, there is little or no information on the usefulness of bedside ketone body monitoring in relation to the time to DKA resolution. The aim of this retrospective study was to determine the clinical value of bedside ketone body monitoring and the factors that affect the time to DKA resolution in patients with T1D.

METHODS

Patients and Data Collection

We extracted the clinical data from the medical records of all T1D cases with DKA admitted to the Department of Pediatrics, Osaka City University, Osaka, Japan, over a period of 10 years from November 2008 to October 2018. Unlike other hospitals, the diabetes team at our Department of Pediatrics manages diabetes patients from infancy to well beyond adulthood. The data of all newly diagnosed and established T1D cases were scanned. The inclusion criteria were (1) T1D diagnosed on the basis of the 1999 World Health Organization criteria [24] and (2) presence of DKA. On the other hand, three exclusion criteria were applied: (1) patients with monogenic diabetes; (2) patients

with severe comorbidities, such as chronic liver diseases, chronic kidney diseases, or chronic heart failure; and (3) patients with missing essential data, such as age, sex, recent HbA1c, pH, serum or urine ketone, and insulin infusion rate. In this study, the number of DKA episodes was counted and used for analysis rather than the number of patients.

Definitions

The diagnosis of DKA was based on the presence of all of the following criteria: (1) blood glucose level (BG) of greater than 300 mg/dL [16.7 mmol/L]; (2) either venous blood pH value of less than 7.30 or serum bicarbonate level of less than 15 mEq/L; (3) bedside 3HB greater than 1.0 mmol/L; and (4) urine ketone positive. DKA severity was classified by venous blood pH level on admission [25]: (1) mild for pH between 7.25 and 7.30; (2) moderate for pH between 7.00 and 7.24; and (3) severe for pH below 7.00. The anion gap was calculated as serum bicarbonate level (mmol/L) minus serum sodium level (mEq/L) minus serum chloride level (mEq/L). Recovery from DKA (DKA resolution) was defined as 3HB below 1.0 mmol/L for the first time since the commencement of DKA therapy. Consciousness was assessed by the Glasgow Coma Scale (GCS), and exacerbation of impaired consciousness was considered as GCS score of discretion more than twice that recorded on admission. Severe hypoglycemia was defined as a decrease in BG level below 70 mg/dL that required urgent medical treatment, such as glucose infusion and glucagon use. Mild hypoglycemia was defined as a decrease in BG level below 70 mg/dL associated with recovery following management by the patients themselves. All complications were recorded as necessary. Data of all clinical outcomes were obtained from the clinical records during admission for DKA treatment. The time to DKA resolution was defined as the time period from the start of insulin infusion until the fall of 3HB level to less than 1.0 mmol/L. The total insulin dose was calculated from clinical chart data and represented the sum of all insulin infusion doses administered until DKA resolution.

Measurements

On admission, all patients underwent standard clinical examination, including GCS, respiratory rate, pulse rate, capillary refill, assessment of dehydration, and routine blood biochemical tests, such as BG, serum electrolytes, and pH. All DKA-suspected cases underwent measurements of finger-prick capillary BG and 3HB using a bedside strip meter (Freestyle Precision Xceed; Abbott Japan, Chiba, Japan) [26]. The vital signs (consciousness level, body temperature, arterial blood pressure, heart rate, and respiratory rate) were checked hourly, while the biochemical data (BG and 3HB levels) were measured every 2–3 h until DKA resolution. Venous blood gases and other laboratory tests were conducted when necessary, depending on the clinical condition.

Management and Treatment Target

The main aim of DKA treatment was the resolution of ketonemia and prevention of hypoglycemia. Towards this goal, the infusion rates of glucose and insulin were selected to reduce the level of 3HB, but not BG level. Briefly, the designated primary infusion solution was 0.9% normal saline to correct dehydration, with the infusion rate set to 10 ml/kg/h for the first 1 h and changed appropriately thereafter if clinically needed. Insulin was infused intravenously at the start of DKA treatment with the aim of increasing serum insulin and correcting insulin deficiency. The selected initial insulin dose was at least 0.1 units/kg/h and increased if BG level or 3HB remained high. The glucose infusion rate (GIR) was adjusted to maintain BG target above 200 mg/dL to avoid hypoglycemia. If the BG level decreased faster than 100 mg/dL/h, the insulin infusion rate was halved, or GIR was increased by 2.0 from 1.0. Although BG level fell below 70 mg/dL with sufficient GIR, insulin infusion was stopped temporarily, followed immediately by intravenous injection of 10 g glucose and/or 10 g orally administered glucose. Potassium was usually added to the primary infusion solution at a concentration of up to 40 mEq/L unless the patient had severe hyperkalemia (i.e., serum K^+ above 7.0 mEq/L).

Subcutaneous basal insulin injection was implemented before finishing intravenous insulin infusion. The pediatric diabetes team discussed and managed the DKA treatment plan each day and night; however, the on-site physician made the final decision based on the clinical status.

Study Outcome

The primary outcome in this study was the assessment of the relationship between various clinical and laboratory factors and time to DKA resolution. The secondary outcome was the insulin dose until DKA resolution.

Statistical Analysis and Ethical Compliance

Biochemical data showed skewed distribution patterns and thus these variables were reported as median and quartile. The skewed data of each group recorded at specific time points were compared using the Wilcoxon rank-sum test. The relationship between the time to DKA resolution and each variable was examined using Spearman rank correlation analysis. The hourly changes in BG and 3HB concentrations from admission to 5 h were expressed as interquartile ranges (25th–75th percentiles). All *P* values were two-tailed, and values less than 0.05 were considered significant. All statistical analyses were performed using Stata SE software, version 16.1 (Stata Corp., College Station, TX).

The study protocol was approved by the Human Ethics Committee of Osaka City University Graduate School of Medicine (#4244) and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Given the retrospective design of the study, no medical, pharmacological, or behavioral interventions were involved. Informed consent was obtained in the form of opt-out on the website. Those who rejected were excluded. Eventually, nobody rejected the participation.

RESULTS

Supplementary Fig. 1 illustrates the protocol followed for the selection of patients in this study. Briefly, 100 episodes that were hospitalized for suspected DKA were identified from the medical records of 636 patients with T1D. We excluded 48 episodes with missing critical data related to DKA diagnosis (e.g., blood pH and 3HB level on admission). Of the remaining 52 episodes, four patients developed DKA twice, and two patients developed DKA three times. Thus, the present study included initially 52 episodes in 44 patients who fulfilled the inclusion and exclusion criteria defined for this study. However, two episodes in two patients had gastroenteritis during the course of the study and their data were therefore excluded from further analysis. All cases were Japanese.

The demographic characteristics of the study subjects are shown in Table 1. Almost a quarter of the cases were newly diagnosed T1D cases, while the other patients had already been diagnosed with T1D previously. None of the patients had or developed severe complications, such as organ failure, cerebral edema, or death. Of the 52 patients, 20 developed mild episodes of hypoglycemia during insulin infusion, which were corrected with oral glucose intake.

With regard to insulin treatment, the initial insulin dose per kilogram body weight and the required insulin dose per kilogram body weight until DKA resolution were significantly higher in the newly diagnosed cases than in the established cases. All the newly diagnosed cases were enrolled in educational classes about T1D during the same hospitalization. For this reason, the duration of hospitalization was about three times longer for the newly diagnosed group than that of the established group. The median time to DKA resolution was 11.0 h in the newly diagnosed cases and 10.0 h in the established cases, and the difference in this parameter between the two groups was not significant. All cases completed DKA treatment while inpatients in a general pediatric ward setting, and none required intensive care during the DKA treatment period.

Table 1 Baseline characteristics of participants divided into patients with newly diagnosed and established type 1 diabetes (T1D)

	Total *n* = 52	Newly diagnosed *n* = 13	Established cases *n* = 39	*P* value
Male patients (%)	20 (38)	5 (38)	15 (38)	1.000
Body weight (kg)	48.0 (36.7–56.6)	30.0 (13.0–40.0)	53.9 (44.1–59.5)	< 0.001
HbA1c (NGSP%)	11.0 (8.8–13.4)	13.0 (11.3–14.5)	10.7 (8.5–12.0)	0.003
Clinical history				
Age at T1D diagnosis (years)	8.0 (4.0–11)	11 (2.5–12.5)	8.0 (4.0–10)	0.256
DKA onset age (years)	15 (11–19)	11 (2.5–12.5)	17 (13–20)	< 0.001
Underlying reason for DKA (%)				
First onset	13 (25)	13 (100)	–	–
Insulin omission	10 (19)	–	10 (26)	–
Pump troubles	22 (42)	–	22 (56)	–
Sick days	7 (13)	–	7 (18)	–
Laboratory data on admission				
BG (mg/dl)	409 (336–530)	492 (328–705)	408 (339–498)	0.201
3HB (mmol/l)	5.8 (5.1–6.6)	6.3 (5.35–7.35)	5.6 (5.0–6.3)	0.081
pH	7.17 (7.11–7.22)	7.17 (7.11–7.20)	7.17 (7.10–7.23)	0.634
DKA severity				
Mild	8 (15)	2 (15)	6 (15)	0.862
Moderate	41 (79)	10 (77)	31 (79)	–
Severe	3 (6)	1 (8)	2 (5)	–
Treatment				
Initial insulin dose for DKA treatment (units/kg/hr)	0.19 (0.10–0.30)	0.27 (0.20–0.33)	0.15 (0.10–0.23)	0.0070
Required insulin dose until 3HB < 1.0 mmol/L (units/kg)	1.30 (0.80–1.88)	2.65 (1.07–2.84)	1.25 (0.79–1.52)	0.0066
Clinical course				
Time to 3HB < 1.0 mmol/L (h)	10.3 (8.0–13.8)	11.0 (8.25–14.25)	10.0 (7.0–14.0)	0.743
Highest BG (mg/dl)	477 (403–586)	616 (476–716)	450 (369–521)	0.003
Lowest BG (mg/dl)	89 (52–161)	87 (38–166)	90 (58–162)	0.380
Duration of venous insulin infusion (h)	15.5 (11–19)	12.0 (7.0–18.5)	18.0 (8.0–20.75)	0.166

Table 1 continued

	Total *n* = 52	Newly diagnosed *n* = 13	Established cases *n* = 39	*P* value
Initiation of subcutaneous basal insulin injection (h)	13.5 (8–19)	18 (9–19)	12 (7–18.5)	0.285
Oral intake time (h)	13.5 (7.4–18.9)	9.0 (3.25–20.0)	14.0 (9.0–18.5)	0.320
Duration of hospitalization (day)	2.0 (0.82–6.0)	6.07 (4.08–7.3)	1.2 (0.69–2.7)	< 0.001
Complications				
Death	0	0	0	–
Consciousness exacerbation	0	0	0	–
Organ failure	0	0	0	–
Respiratory issues	0	0	0	–
Mild hypoglycemia	20	6	14	0.515
Severe hypoglycemia	0	0	0	–

Data are *n* (%) or median (25th–75th percentiles)

DKA diabetic ketoacidosis, *3HB* serum 3-hydroxybutyrate, *BG* blood glucose

Severe hypoglycemia was defined as BG level decreased under 70 mg/dL and need emergency medical treatment such as glucose infusion and glucagon use. Mild hypoglycemia was defined as BG level decreased below 70 mg/dL and recovered following treatment by patients themselves

The relationships between the time to DKA resolution and various parameters, including blood pH level, are shown in Supplementary Table 1 and Fig. 1. The blood pH and BG levels on admission did not correlate significantly with the time to DKA resolution. In contrast, 3HB on admission correlated significantly with the time to DKA resolution in the newly diagnosed group but not the established group (Fig. 1a). There was no significant relationship between the insulin dose and the time to DKA resolution in the established group. The median value of the required insulin dose per kilogram body weight kg was 1.25 (mainly distributed below 2.0 units per kg body weight in the established group) (Fig. 1b).

We also analyzed the relationship between blood pH and 3HB levels on admission and the time to DKA resolution (Fig. 2). The results showed that the time to DKA resolution did not correlate significantly with any of the two parameters in the newly diagnosed and established groups.

Finally, we examined the relationship between blood pH and bedside 3HB using all the measurements conducted in this study in the 52 episodes, independent of the time of admission ($n = 90$) (Supplementary Fig. 2). 3HB levels correlated significantly with blood pH levels, and the patients who showed normalization of 3HB levels (red symbols in the figure) also had normalized pH levels. Of these, three patients continued to show apparent acidemia (encircled data). The average pH in these cases was below 7.3, but they had suffered gastroenteritis with fever and diarrhea at the time of these measurements. These findings suggested that the delay in recovery of symptoms and pH was affected by gastroenteritis. Analysis of the relationships between the time to DKA resolution and various parameters after excluding the aforementioned two outlier cases (Supplementary Fig. 2) did not alter the results (shown in Supplementary Table 2).

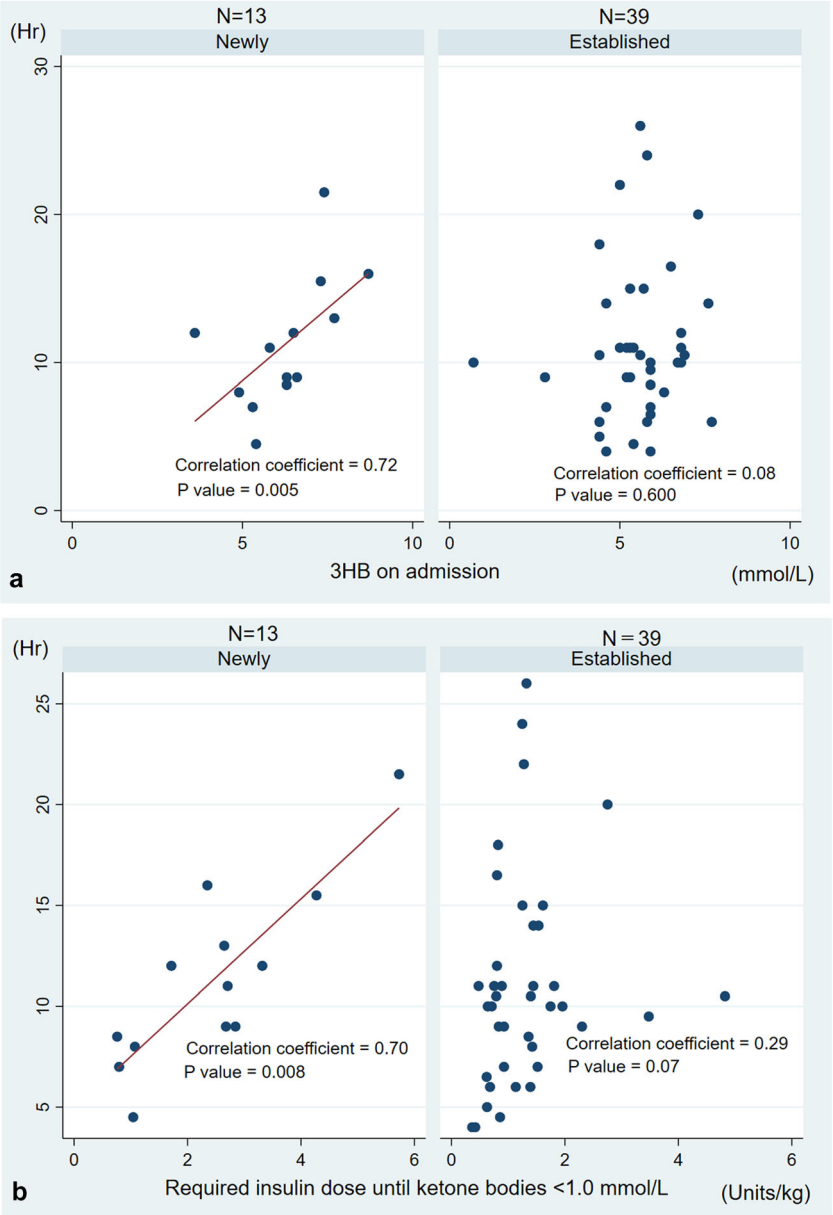

Fig. 1 Relationship between **a** DKA resolution time and 3HB on admission. **b** DKA resolution time and required insulin dose for DKA resolution (per body weight kg), in newly diagnosed and established cases of T1D. Regression lines were calculated by linear regression analysis. Only patients with newly diagnosed T1D showed significant positive relationship. DKA resolution represented the time at which 3HB level was below 1.0 mmol/L. *P* values by Spearman correlation analysis. DKA diabetic ketoacidosis, 3HB serum 3-hydroxybutyrate

DISCUSSION

Our study demonstrated that DKA treatment protocol guided by bedside 3HB measurement allowed complete resolution of DKA within a median of 10–11 h, without severe complications, apart from mild hypoglycemia. Interestingly, neither the time to DKA resolution nor 3HB on admission correlated significantly with blood pH level. In contrast, 3HB on admission correlated significantly with the time to DKA

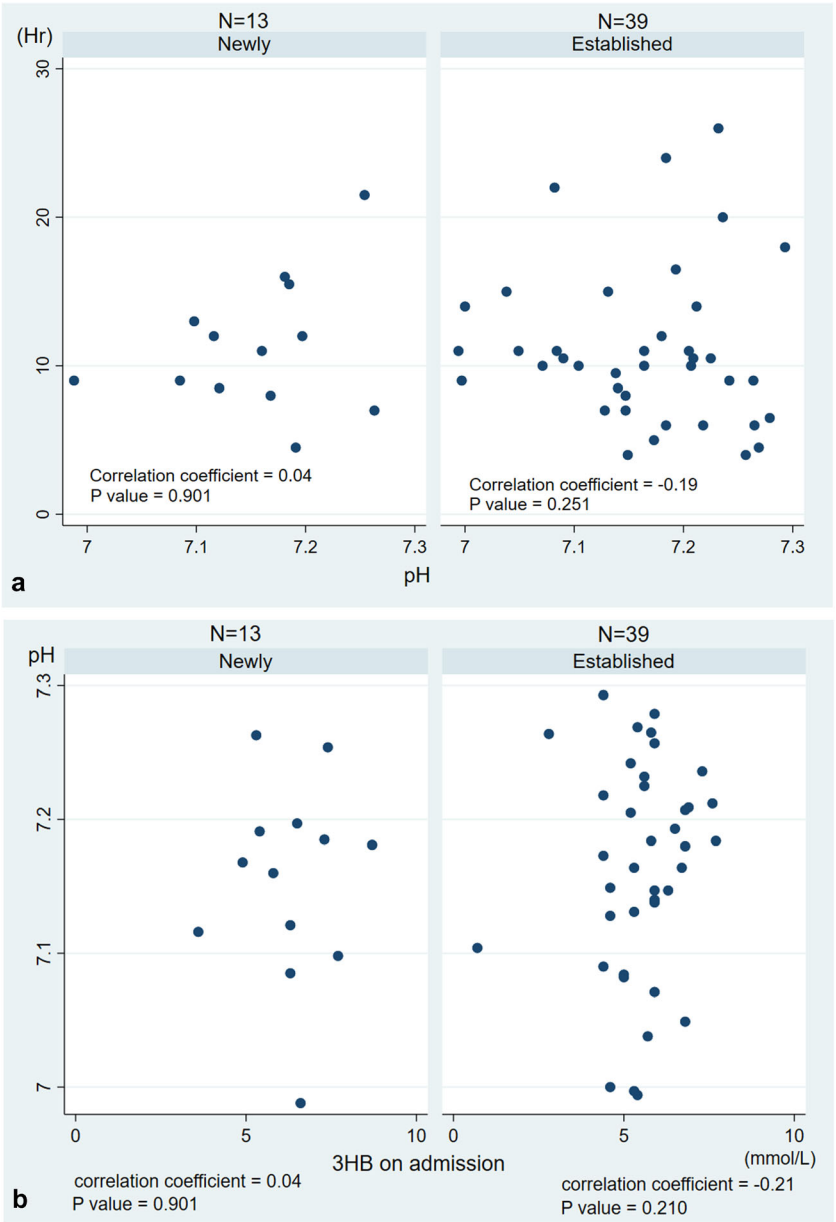

Fig. 2 Relationship between **a** DKA resolution time and blood pH, **b** DKA resolution time and bedside 3HB measured on admission, in newly diagnosed and established cases of T1D. DKA resolution time represented the time at which 3HB level was below 1.0 mmol/L. Regression lines were calculated by linear regression analysis. *P* values by Spearman correlation analysis. 3HB serum 3-hydroxybutyrate

resolution in patients with newly diagnosed T1D.

Blood pH is one of the factors used to assess DKA severity on admission [2]. However, the pH level in this study did not correlate significantly with the time to DKA resolution (Supplementary Table 1, Fig. 1a). On the other hand, 3HB on admission correlated significantly with the time to DKA resolution in patients with newly diagnosed T1D (Supplementary Table 1, Fig. 1b). There was no significant relationship between blood pH and 3HB level on

admission (Fig. 2). This discrepancy could be explained by respiratory compensation for the change in pH. Our results also showed that neither the base excess nor anion gap correlated with 3HB level on admission (Supplementary Table 1). We speculate that ketosis, rather than metabolic acidosis, reflects DKA severity.

DKA resolution can be monitored by various markers, such as blood pH and 3HB, and the treatment target of DKA is still under consideration. The current British Joint Guideline states that bedside monitoring of 3HB could be a more accurate marker for the resolution of acidosis [11]. In the clinical study of diabetic adolescents, Pulungan et al. [22] demonstrated a close and significant correlation between pH and 3HB and that changes in one parameter paralleled that in the other throughout DKA treatment. Furthermore, Noyes et al. [13] reported in their study of 35 patients that bedside changes in 3HB paralleled those in blood pH level and that 3HB fell when the pH level was above 7.30. Similar results were found in our study for the relationship between pH and 3HB (Supplementary Fig. 2). In addition, Kangin et al. [23] reported that normalization of bedside 3HB was associated with early oral fluid intake and allowed the transition to subcutaneous insulin injection. These results suggest that bedside 3HB seems more affordable and convenient for the assessment of DKA response to treatment compared with blood pH.

In this study, DKA resolution was defined as 3HB below 1.0 mmol/L. When 3HB was below 1.0 mmol/L, all patients, except the two patients who developed gastroenteritis, reported resolution of nausea and/or vomiting, with blood pH correction to above 7.3.

Our data also showed that the required insulin dose for DKA resolution was less than 2.0 units/kg in patients with established T1D. Most previous studies described only the initial insulin infusion rate and only some reported the total insulin dosage necessary for DKA resolution. Desse et al. [27] reported that the mean insulin dosage used and time to DKA resolution were 136.85 ± 152.41 units and 64.38 ± 76.34 h. On the other hand, Braatvedt et al. [28] reported the insulin infusion rate used in their 71 DKA adult cases in New Zealand. However, both groups neither mentioned the body weight nor defined the time to DKA resolution. For these reasons, we cannot compare our data with any of the aforementioned previous studies. We recommend further studies to determine the relationship between the rate of insulin administration, total insulin dosage, and the time to DKA resolution.

The time to DKA resolution was longer in the T1D established group than in the newly diagnosed group and did not correlate with 3HB on admission. This finding could be due to different mechanisms involved in the pathophysiology of DKA in patients with established T1D, such as infection, insulin omission, and insulin pump infusion troubles, as discussed below. Apart from insulin deficiency, other factors such as infection might also play a role in the observed delay in DKA resolution.

How can one explain the significant relationship between 3HB on admission and time to DKA resolution in patients with newly diagnosed T1D? While our study design did not provide an answer to this important question, it is noteworthy that the reported time required to secure DKA resolution varied widely from one study to another. We limited our literature search to studies that defined DKA resolution as a fall in 3HB [13, 20–23, 26–28]. On the basis of these studies, it seems that the 3HB level on admission could be a significant predictor of the time to DKA resolution.

The strengths of the present study include a detailed analysis of the relationship between time to DKA resolution and various clinical parameters. However, our study has certain limitations. First, the study was retrospective in design, and thus it does not allow conclusions on the effects of bedside 3HB-use-policy on time to DKA resolution. However, our treatment protocol can potentially be the cornerstone of future prospective studies designed to verify such a relationship. Second, our study assessed only patients admitted to the hospital. Such patients could have several clinical issues, such as the severity of T1D, treatment delay, and infection-related complications that may overestimate the time to DKA resolution. Further studies of outpatients are necessary to confirm the present results and identify bias if any.

Lastly, the endpoint of DKA resolution in this study was defined as 3HB level below 1.0 mmol/L. There is still no definite agreement on the best parameter that accurately reflects DKA resolution, especially the choice between blood pH and 3HB. Our data shown in Supplementary Table 1 suggest no significant relationship between blood pH and time to DKA resolution. In this regard, several studies discussed the usefulness of 3HB monitoring in DKA [12–14, 21]. Our study adds support to the benefit of 3HB as a valuable marker for DKA resolution compared with blood pH level. Further prospective studies are necessary to confirm the true value of 3HB.

CONCLUSION

Our study suggested that bedside 3HB monitoring is potentially useful for determining the time to DKA resolution in patients with T1D free of severe complications. The study also indicated that 3HB, but not blood pH, correlated significantly with the time to DKA resolution in patients newly diagnosed with T1D. Further studies are needed to confirm the utility of 3HB in assessing the time to DKA resolution in patients with T1D.

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Authors' Contributions. All authors identified the need for this study, helped develop the search terms used, and screened the search results. All authors discussed the results and reviewed the different drafts of the manuscript and approved the final version for submission. TK reviewed the manuscript for medical accuracy on behalf of YY.

Disclosures. The authors Yoshihiko Yuyama, Tomoyuki Kawamura, Naoko Nishikawa-Nakamura, Yuko Hotta, Kayako Hashimura, Tomomi Hashimoto, Masakazu Hirose, Takashi Higashide, and Takashi Hamazaki declare no conflict of interest in relation to this study.

Compliance with Ethics Guidelines. The study protocol was approved by the Human Ethics Committee of Osaka City University Graduate School of Medicine (#4244) and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Given the retrospective design of the study, no medical, pharmacological, or behavioral interventions were involved. Informed consent was obtained in the form of opt-out on the website.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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