Clinical characteristics and outcomes of patients with diabetic ketoacidosis of different severity

Ying Wei, MS, Chushan Wu, MD, Feiya Su, MS, Han Zhang, MS, Jinxia Zhang, MS, Rongxiu Zheng, MD

Abstract
To analyze the influencing factors and outcomes of the different severity of diabetic ketoacidosis (DKA).

A total of 50 children with DKA admitted to the Department of Pediatrics, Tianjin Medical University General Hospital from January 2009 to December 2018 were included in this study. The patients were divided into mild group, moderate group, and severe group according to the severity of the disease. We then analyzed the clinical characteristics and outcomes of the 3 groups.

Compared to mild and moderate DKA groups, patients with severe DKA were more likely to present chest tightness, and higher levels of blood osmotic pressure, urea, and creatinine (P < .05). Logistic regression analysis showed that blood osmotic pressure, creatinine, and chest tightness were independent factors for severity of DKA. There was a significant difference in the resolution time of DKA among the 3 groups (mild vs moderate: 9.0 hours vs 15.25 hours; moderate vs severe: 15.25 hours vs 24.5 hours, P < .001). There were statistical differences in the decline of Glasgow score among 3 groups (P = .004).

Patients with severe DKA showed higher osmotic pressure and creatinine, as well as dyspnea. The children with severe DKA were more likely to present progression of neurological symptoms, which was necessary to pay attention to the presence of brain edema.

Abbreviations: DIC = disseminated intravascular coagulation, DKA = diabetic ketoacidosis, DM = diabetes mellitus, ECG = Electrocardiography.

Keywords: blood osmotic pressure, brain edema, diabetes mellitus, diabetic ketoacidosis

1. Introduction
The prevalence of diabetes mellitus (DM) in children shows a tendency of elevation worldwide, which severely affect their growth and health.1] The pathogenesis of DM is mainly associated with the genetic background, environment, autoimmunity, and insulin resistance, which finally leads to functional failure of pancreatic β cells, as well as decline in the secretion of insulin. According to the International Diabetes Federation Diabetes Atlas for the global estimate of the DM prevalence for 2017,[2] there were a total of 586,000 children and adolescents with type I DM. Besides, about 96,000 children and adolescents aged less than 15 years are newly diagnosed with DM, with an annual increase of about 3%.

Diabetic ketoacidosis (DKA), a common complication for DM in children,[3] is featured by hyperglycemia, ketosis, metabolic acidosis, and dehydration. It shows a rapid onset, quick progression and severe conditions, with a mortality of 5%.[4] Therefore, it is necessary to identify new and effective markers for the evaluation of DKA conditions, which is of prime importance to the screening of high risk patients and proper treatment. However, rare studies have been focused on it in pediatric fields. In this study, we aim to investigate the influencing factors and outcomes of patients with different severity of DKA.

2. Materials and methods
2.1. Subjects
In this study, we included patients admitted to the department of pediatrics in our hospital between January 2009 and December 2018. The inclusion criteria were as follows: those diagnosed with DM or DKA; those with complete clinical records including biochemical tests, physical examination, and treatment process. Those with incomplete records or those terminated the study at their will were excluded from this study. Finally, 50 affected children were screened from 140 individuals, and were classified into mild group, moderate group, and severe groups. Then we compared the following parameters using the univariate analysis among the 3 groups: gender, age of diagnosis, a family history of DM, presence of symptoms in the digestive system and nervous system, fatigue, dyspnea, deep respiration, blood glucose, C-peptide level, HbA1c concentration, urea, creatinine, T3 syndrome, hypercholesterolemia, or hypertriglyceridemia. Afterwards, multivariate regression analysis was conducted for the
data with significance. The study was approved by the Ethics Committee of Tianjin Medical University General Hospital.

2.2. Diagnostic criteria

The diagnosis of DM was based on the Standards of Medical Care in Diabetes by American Diabetes Association: ≥6.5%, fasting glucose, ≥7.0 mmol/L; the glucose level in the oral glucose tolerance test at 2 hours was ≥11.1 mmol/L; with typical DM symptoms (e.g., polyuria, polydipsia and weight loss with unknown causes) and random blood glucose level of ≥11.1 mmol/L. DM patients with no definite symptoms were suggested to receive recheck to confirm the diagnosis. DKA was diagnosed based on the diagnostic guidelines proposed by ISPAD criteria: hyperglycemia (blood glucose >11.1 mmol/L; venous pH <7.3 or serum bicarbonate <15 mmol/L; ketonemia (blood β-hydroxybutyrate ≥3 mmol/L) or moderate or large ketonuria. The severity of DKA was categorized by the degree of acidosis: mild: venous pH <7.3 or serum bicarbonate <15 mmol/L; moderate: pH <7.2, serum bicarbonate <10 mmol/L; severe: pH <7.1, serum bicarbonate <5 mmol/L.

2.3. Statistical analysis

SPSS 22.0 software was used for the statistical analysis. Graphpad Prism 8.0 was used for the preparation of charts. Chi-Squared test was performed for the comparison of variables between 2 categorical groups. For the continuous variable, Kolmogorov-Smirnov one-sample test was utilized to test whether the data were normally distributed. The normally distributed data were compared with the Student t test. For the comparison of variables between 2 categorical groups, the Ch-Squared test was performed for the continuous variable, and the statistic was presented as mean ± standard deviation. For the data that were not normally distributed, 2 independent samples were tested based on the non-parametric test, and the statistic was presented as median (25th and 75th percentiles). For the data with statistical difference after univariate analysis, multivariate Logistic Regression analysis was conducted to investigate their potential link.

P value of less than .05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

Fifty DKA children were classified into 3 groups based on blood pH and HCO₃⁻ concentration, including mild group (n = 16), moderate group (n = 16), and severe group (n = 18). There were no statistical differences in the age, age upon diagnosis, family history, presence of symptoms in the digestive system and nervous system, deep respiration, fatigue, C-peptide level, HbA1c concentration, T3 syndrome, hypercholesterolemia, or hypertriglyceridemia among the 3 groups (P > .05). Significant differences were noticed in the dyspnea among the 3 groups (P < .05), especially the patients with severe DKA. In addition, the blood osmotic pressure, urea and creatinine levels in the severe group were significantly higher than that of the moderate group and mild group, respectively (P < .05, Table 1).

3.2. Ordinal logistic regression analysis

In this section, Ordinal logistic regression analysis was conducted using the indices with statistical differences after
univariate analysis as the independent variables, and the DKA conditions as the dependent variables. Our data showed that blood osmotic pressure, creatinine, and dyspnea symptoms could affect the DKA extent, serving as the independent risk factors. Whereas, urea showed no effects on the conditions of DKA in this study (Table 2).

3.3. Treatment efficiency and prognostic analysis of the DKA patients

Fluid infusion was performed for the 50 DKA children upon admission, together with small dose insulin and symptomatic therapy. We then analyzed the DKA resolution time, 24-hour and 48-hour DKA resolution rate, as well as the decline of Glasgow score of the nervous system (Table 3). As shown in Figure 1, there were significant differences in the DKA resolution time within 12 hours in the mild group, moderate, and severe groups (mild group: 9.0 hours; moderate group: 15.25 hours; severe group: 24.5 hours, \( P < .001 \)). For the 24-hour DKA resolution rate, the resolution rate in the mild, moderate, and severe groups were 93.8%, 87.5%, and 44.4%, respectively. There were statistical differences among the resolution rates (\( P < .05 \)). However, there were no statistical differences in the 48-hour resolution rate among the 3 groups (mild group: 100%; moderate group: 93.8%; severe group: 77.8%; \( P > .05 \)).

Among the 50 DKA children, 9 showed disease progression in the nervous system with decline of Glasgow score including 2 in the moderate group and 7 in the severe group, respectively. There were statistical differences among the 3 groups (\( P = .004 \)). Among the 9 cases, 1 showed hypersomnia, elevation of blood pressure, and extension of capillary refill time, which was in a state of coma after admission, together with decline in the heart rate and blood pressure. Unfortunately, the patient died from respiratory and circulating failure and disseminated intravascular coagulation (DIC). The other 8 cases showed satisfactory outcome with no sequela in the nervous system.

4. Discussion

The pathogenesis of DKA is closely related to insufficiency of circulating insulin, which combines with the elevation of blood glucose induced by re-regulation stress hormone, including glucagon, catecholamine, corticosteroid, and growth hormone. In addition, hyperglycemia would induce extracellular osmotic pressure elevation and glucose elevation by osmotic diuresis, as well as electrolyte disturbance and impaired renal function, which then induced glycosogenesis and increase of gluconeogenesis. Lipolysis elevation would lead to generation of free fatty acid, which then resulted in massive acetone body (e.g., acetoacetic acid, \( \beta \)-hydroxybutyric acid, and acetone).\(^{17-19} \) The increase of protein degradation would trigger increase of gluconeogenesis. On this basis, the patients may present hyperglycemia, ketosis, and acidosis. The acetoacetic acid and \( \beta \)-hydroxybutyric acid were strong acids, which would promote the elevation of organic acid concentration. Acidosis patient may present typical Kussmaul respiration. In cases of pH of less than 7.0, they may present central nervous paralysis and severe myasthenia. In addition, the acidic metabolites may induce the dissociation of oxygen from the hemoglobin, which then results in the histanoxia. To our best knowledge, the acidosis may affect the function of central nervous system, which may be related to the hyperosmotic anhydride of the brain cells.\(^{10} \)

Our data showed that blood osmotic pressure was an independent risk factor for severe DKA. In a previous study, the blood osmotic pressure in the children with moderate and severe DKA was significantly higher than that with mild DKA, together with a higher tendency of higher blood glucose and higher osmotic pressure.\(^{11} \) In adults, high blood osmotic pressure was a risk factor for the DKA mortality.\(^{12} \) Besides, a high osmotic pressure was considered a risk factor for brain edema.\(^{13} \) High concentration of blood glucose may induce osmotic diuresis. Generally, an elevation of blood glucose of 5.6 mmol/L may predict an increase of blood osmotic pressure of 5.5 mmol/L. Then it would trigger the flow of liquid from the cells outside of the cells, which then induced cellular dehydration,

### Table 2

| Variable                  | B   | SE  | Wald | P    | OR  | Lower limit | Upper limit |
|---------------------------|-----|-----|------|------|-----|-------------|-------------|
| Blood osmotic pressure    | 0.048 | 0.024 | 3.930 | .047 | 1.049 | 1.001 | 1.100 |
| Urea                      | -0.220 | 0.218 | 1.014 | .314 | 0.803 | 0.523 | 1.231 |
| Creatinine                | 0.074 | 0.027 | 7.517 | .006 | 1.077 | 1.021 | 1.135 |
| Dyspnea                   | 2.013 | 0.934 | 4.645 | .031 | 7.486 | 1.200 | 46.712 |

### Table 3

| Variable                  | Mild group (n = 16) | Moderate group (n = 16) | Severe group (n = 18) | P value |
|---------------------------|--------------------|------------------------|-----------------------|---------|
| Time of DKA resolution, h | 9.0 (8.0, 11.75)   | 15.25 (6.5, 18.91)     | 24.50 (18.64, 36.50)  | < .001  |
| Without DKA resolution within 24 h | 1 (6.2%) | 2 (12.5%) | 10 (55.6%) | .002  |
| Obtained DKA resolution within 24 h | 15 (93.8%) | 14 (87.5%) | 8 (44.4%) | .004  |
| Without DKA resolution within 48 h | 0 (0%) | 1 (6.2%) | 4 (22.2%) | .081  |
| Obtained DKA resolution within 48 h | 16 (100%) | 15 (83.8%) | 14 (77.8%) | .004  |
| No decline of Glasgow score | 16 (100%) | 14 (87.5%) | 11 (61.1%) | .004  |
| With decline of Glasgow score | 0 (0%) | 2 (12.5%) | 7 (38.9%) | .004  |
especially occurrence of DKA combined with high blood glucose and high osmotic pressure. This would lead to a higher mortality, together with presence of nervous system complications and multi-organ dysfunction. Therefore, for the DKA children, blood osmotic pressure is an important index for the establishment of treatment regimen, in the presence of condition evaluation and prediction of nervous system complications. In this study, patients with severe diseases showed higher creatinine, which was a risk factor for DKA similar with the previous description. In addition, according to a recent meta-analysis, creatinine was also associated with poor outcomes in DKA patients. The elevation of creatinine indicated decline of blood volume, and renal hypoperfusion, which reflected the severity of dehydration and the secondary target organ damages. In this study, children with severe DKA showed a higher tendency of dyspnea compared with the others. Multiple studies indicated that dyspnea was a complicated condition for DKA. Some patients were usually misdiagnosed as they only presented dyspnea and shortness of breath. Meanwhile, patients with a burst-type I DM combined with DKA usually showed dyspnea symptoms. In this study, part of the patients with dyspnea received cardiac creatase determination and ECG examination, among which some showed elevation of creatase. However, it was not associated with the disease conditions, and there were no aberrant changes in the ECG. Taken together, a high blood osmotic pressure, creatinine level, and dyspnea symptoms may indicate dehydration, histoxia, renal dysfunction, and even CNS function. All these would lead to progression of DKA.

In this study, there were statistical differences in the resolution time of DKA among the 3 groups ($P<.001$). To our best knowledge, rare studies have focused on the resolution time of DKA in different severity. In a previous study, the resolution time for DKA therapy was $16.91 \pm 4.223$ hours. In this study, the whole DKA median resolution time was 16.25 hours, which was similar with the previous study. However, we illustrated the DKA resolution time for different groups with various severity. Oettingen et al. reported that the resolution time for mild, moderate, and severe DKA patients was 6.9 hours, 8.2 hours, and 14.5 hours, respectively. Compared with their findings, the median DKA resolution time in our study was relatively longer, which may be related to the fact that the majority of the children in our study received the balanced infusion according to the proposed guideline by Chinese Medical Association, in order to bring down the prevalence of brain edema. Oettingen et al did not emphasize the liquid infusion. We speculated that it may be related to the fact that rapid infusion may short the DKA resolution time, however, it may lead to higher possibility of brain edema. In this study, patients with severe DKA showed longer DKA resolution time.
resolution time. Within 24 hours after admission, the resolution time for DKA children in the mild group and moderate group was 93.8% and 87.5%, which was significantly higher than that of the patients with severe DKA (93.8% vs 44.4%, P<.05; 87.5% vs 44.4%, P<.05). About 48 hours after admission, there were no statistical differences in the resolution time among the 3 groups (P>.05). Interestingly, part of the patient showed progression of the nervous system dysfunction during the DKA resolution. In this study, there were statistical differences in the Glasgow score decline among the 3 groups (P=.004). Such difference occurred at 0.4 to 4 hours, especially at 3 to 4 hours. For the children with such condition, attention should be paid to the brain edema. As previously described, most of the DKA related brain edema occurred about 20 hours after onset of DKA with a median time of 3.5 hours (1.5–20.0 hours),[18] which was similar with our results. Brain edema is a severe complication of DKA. In a recent survey in Britain, the prevalence of brain edema was 6.8/1000.[19] In a multicentered study in US, the prevalence of brain edema among the DKA patients was 0.9%.[20] While the prevalence in the children was even higher than that of the adults. Moreover, DKA patients newly diagnosed with DMA showed a higher prevalence of brain edema, and the mortality rate was about 25%. Meanwhile, 35% of the survivors showed sequela in the nervous system.[19] To date, the exact mechanism of brain edema among DKA patients is still not well defined. Previously, it may be related to the rapid decline of serum osmotic pressure during the intravenous infusion.[21,22] Nevertheless, there were no obvious correlation between the prevalence and mortality of brain edema and the dripping velocity and osmotic pressure. In addition, brain edema was correlated with the ischemia-reperfusion injury of the brain cells. In clinical settings, special care should be taken during the management of DKA. In cases of brain edema, immediate treatment should be given to bring down the mortality of brain edema.

Indeed, there are some limitations in this study. Firstly, this was a retrospective study. For the patients with nervous system dysfunction, we could not collect their fundus examination and cranial imaging findings. Secondly, we could not comprehensively analyze the diagnosis and imaging outcomes of the brain edema patients.

In summary, patients with severe DKA showed higher osmotic pressure and creatinine, as well as dyspnea symptoms. Patients showed longer resolution time of DKA if they present severe conditions. Those with moderate or severe DKA may present progression in the nervous system symptoms, and much attention should be paid to the brain edema. Immediate treatment regimen should be given in order to bring down the mortality.

Author contributions

Data curation: Chushan Wu.
Formal analysis: Feiya Su.
Methodology: Han Zhang.
Software: Jinxia Zhang.
Writing – original draft: Ying Wei.
Writing – review & editing: Rongxiu Zheng.

Correction

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