Annals of Clinical and Analytical Medicine
Original Research

Evaluation of factors associated with time to diabetic ketoacidosis resolution in children

Factors associated with diabetic ketoacidosis resolution time

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Abstract
Aim: In this study, it was aimed to examine the relationship between clinical, demographic, and laboratory characteristics of patients at admission and time to diabetic ketoacidosis (DKA) resolution.
Material and Methods: The files of patients with the diagnosis of DKA between January 2013 and December 2018 were reviewed retrospectively.
Results: A total of 25 patients were included in the study. The mean age of the patients was 9.3 ± 3.41 years. In 19 patients (76%), diabetes mellitus (DM) was diagnosed simultaneously with DKA. The mean time to DKA resolution was found to be significantly longer among patients with a family history of DM, newly diagnosed DM, respiratory distress, odor of acetone on the breath, altered consciousness, and severe coma. There was a significant correlation between the time to DKA resolution and the Pediatric Risk of Mortality score and the length of stay. There was also a significant negative correlation between time to DKA resolution and both pH and HCO3 levels.
Discussion: DKA is an acute, severe, and life-threatening complication of type 1 DM in children. It is important to identify the factors affecting the prognosis and resolution time of comas in these patients in order to predict outcomes. Our findings show that the prognosis will be worse and the time to resolution will be longer among children with altered consciousness, newly diagnosed DM, respiratory distress, a high PRISM score, severe DKA coma, and severe acidosis at the time of admission.

Keywords
Children, Coma, Diabetic Ketoacidosis (DKA), Factors, Pediatric, Resolution Time

DOI: 10.4328/ACAM.21164 Received: 2022-03-28 Accepted: 2022-06-02 Published Online: 2022-08-01
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Introduction

Diabetic ketoacidosis (DKA) is an acute, severe, and life-threatening complication of type 1 diabetes mellitus (DM) in children. Although there have been improvements in the treatment and care of type 1 DM, DKA continues to be a major cause of hospitalization and the leading cause of death in children with type 1 DM [1,2]. Overall mortality in children with DKA varies from 0.15% to 0.35% in developed countries, and from 3.4% to 12.7% in developing countries [3-8].

The main lines of DKA treatment are as follows: supportive measures, clinical and biochemical monitoring, rehydration with isotonic saline, intravenous insulin therapy, and potassium supplementation [9,10]. With these forms of management, it is expected that patients will recover and DKA will resolve. However, both physicians and families want to estimate patient outcomes and time to DKA resolution with data at admission. There is a limited number of studies on this subject in the literature [6, 11], and sharing related experiences will increase awareness of the topic. For this purpose, in this study, it was aimed to examine the relationships between clinical, demographic, and laboratory characteristics of patients at admission and time to DKA resolution.

Material and Methods

Between January 2013 and December 2018, 30 DKA patients were admitted to the pediatric intensive care unit (PICU) of Adiyaman University Training and Research Hospital. Two patients died and were excluded from the study. Three patients were excluded because their records were missing data. Patient files were scanned in detail in terms of clinical, demographic, and laboratory features at the time of admission. The study was approved by the ethics committee of Adiyaman University (2018/2-29).

DKA diagnosis was defined according to the criteria established by the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus of 2014, including blood glucose greater than 200 mg/dL, venous pH less than 7.3, or bicarbonate less than 15 mmol/L and ketonemia or ketonuria [12]. ISPAD 2014 guidelines were used to define DKA severity categories. Three groups were defined: (1) mild (venous pH < 7.3 or bicarbonate < 15 mmol/L), (2) moderate (pH < 7.2 or bicarbonate < 10 mmol/L), and (3) severe (pH < 7.1 or bicarbonate < 5 mmol/L).

Time to DKA resolution was defined as the interval in hours between the first vascular filling to treat the DKA and DKA resolution, defined as clinical improvement (normal vital signs, oral feeding tolerance without emesis, and full consciousness), pH greater than 7.3, bicarbonate greater than 15 mmol/L, and/or closure of the anion gap.

Statistical analyses were performed using SPSS for Windows version 23.0 (SPSS Inc, Chicago, IL, US). Descriptive statistics were calculated, and categorical variables were analyzed using the Chi-square test. The independent two-sample t-test was used to compare the quantitative variables and to analyze the differences between means. A one-way analysis of variance (ANOVA) test was used for evaluations involving more than two groups. The relationships between continuous data and time to DKA resolution were evaluated using the Pearson correlation test. Multivariate logistic regression (enter model) was performed to determine the independent factors affecting the time to DKA resolution. Then, the factors that were found to be significant in the multivariate logistic regression (enter model) were compared with the multivariate logistic regression (backward model). P-values less than 0.05 were considered statistically significant.

Results

Demographic features

A total of 25 patients were included in the study. The mean age of the patients was 9.3 ± 3.41 years (range 2–15 years). Eight (32%) of our patients were female and 17 (68%) were male. Fifteen patients (60%) were residing in the city center, seven patients (28%) lived in the district, and three patients (12%) lived in villages. Seven patients (28%) were admitted to the hospital in the spring, two patients (8%) were admitted in the summer, ten patients (40%) were admitted in the autumn, and six patients (24%) were admitted in the winter. Among 19 patients (76%), DM was diagnosed simultaneously with DKA. Four patients (11.1%) had a family history of DM.

The relationship between demographic characteristics and time to DKA resolution was examined (Table 1). The time to DKA resolution was longer among females living in the city center and presenting in the spring season, but these differences were not statistically significant. The mean time to DKA resolution was significantly longer among patients with a family history

Table 1. Relationship between basic demographic features and time to DKA resolution

Parameter	Time to DKA resolution (Hours)	p
Gendera		
Male (n=17)	18,79±10,57 (9-45)	0,419
Female (n=8)	23,13±15,49 (9-53)	
Place of residenceb		
City center (n=15)	21,27±14,31 (9-53)	0,816
District (n=7)	19,50±9,76 (12-41)	
Villiage (n=3)	16,33±5,69 (10-21)	
A history of chronic illnessa		
Yes (n=3)	15,66±6,11	0,586
No (n=22)	20,79 ±12,76	
Newly diagnosed DM patientsa	24.96± 12,06	0.044*
Previously diagnosed DM patients	15,0±4,04	
Presence of consanguinity between parentsa		
Yes (n=5)	13,70±5,35	0,143
No (n=20)	21,80±12,95	
The presence of a family history of DMa		
Yes (n=4)	31,25±13,72	0,037*
No (n=21)	18,07±11,003	
Admission seasonb		
Spring (n=7)	24,29±16,35 (10-53)	0,708
Summer (n=2)	13,50±6,37 (9-18)	
Autumn (n=10)	19,00±9,57 (9-41)	
Winter (n=6)	19,58±13,25 (9-45)	

* p <0.05; a, Independent Student T test, mean ± SD; b, One-Way ANOVA, mean ± SD; DM, Diabetes mellitus; DKA, diabetic ketoacidosis

Table 2. Patients' clinical characteristics

Parameter	n (%)
Complaints	
Polydipsia	20 (80)
Polyuria	19 (76)
Respiratory distress	11 (44)
Weight loss	8 (32)
Polyphagia	3 (12)
Odor of acetone on the breath	2 (8)
Number of DKA attacks	
First	23 (92)
Second	1 (4)
Third	1 (4)
State of consciousness	
Normal	15 (60)
Confused	10 (40)
Severity of DKA coma	
Mild	8 (32)
Modarete	8 (32)
Sever	9 (36)
Systolic blood pressure (mmHg) [mean±SD (min-max)]	114,44±15,34 (91-150)
Diastolic blood pressure (mmHg) [mean±SD (min-max)]	69,70±13,08 (41-90)
Focus of infection	
Yes	2 (8)
No	23 (92)
PIM [mean±SD (min-max)]	1,00±0,19 (0,8-1,4)
PRISM [mean±SD (min-max)]	7,22±2,88 (1,5-18,7)
Complications	
Hypopotasemia	3 (12)
Cerebral edema	1 (4)
Sepsis	2 (8)
Septic shock	3 (12)
Intensive care stay (hours) [mean±SD (min-max)]	36,37±9,09 (14-57)

DKA: diabetic ketoacidosis, PIM: Pediatric Index of Mortality, PRISM: Pediatric Risk of Mortality

Table 3. Relationship between clinical features and time to DKA resolution

Parameter	Time to DKA resolution (hours)	p
Respiratory distress [a]		
Yes	26,5556±15,51702	0,047*
No	16,5938±8,44831	
Odor of acetone on the breath[a]		
Yes	37,0000±22,62742	0,039*
No	18,7174 ±10,53439	
Number of DKA attacks		
First	20,3261±12,70255	0,725
Reccurent	18,5000±3,53553	
State of consciousness[a]		
Normal	15,2667±8,26755	0,006*
Confused	27,5500±13,76883	
Severity of DKA coma[b]		
Mild	12,5000±3,96412	0,018*
Modarete	19,2500±9,75046	
Sever	27,8333±14,94574	

* p<0,05; a: Independent Studen T test, b: One-Way ANOVA, DKA: Diabetic ketoacidosis

of DM (p = 0.037) and newly diagnosed with DM (p = 0.044). Although the time to DKA resolution was higher among younger patients, the correlation between the variables was not significant (r = 0.055, p = 0.794).

Clinical features

The most common complaints were polydipsia (80%) and polyuria (76%). While 23 patients (92%) presented with their first DKA attack, one patient presented with a second attack and one patient with a third attack. Ten patients (40%) were unconscious at admission. Eight patients (32%) presented with mild DKA, eight patients (32%) with moderate, and nine patients (36%) with severe DKA. Mean systolic blood pressure was 114.44 ± 15.34 mmHg (range 91–150 mmHg), and mean diastolic blood pressure was 69.70 ± 13.08 mmHg (range 41–90 mmHg). The mean Pediatric Index of Mortality (PIM) score was 1.00 ± 0.19 (range 0.8–1.4), and the mean Pediatric Risk of Mortality (PRISM) score was 7.22 ± 2.88 (range 1.5–18.7). The mean length of stay in the PICU was 36.37 ± 19.09 hours. The clinical characteristics of the patients are presented in Table 2. The relationship between clinical features and time to DKA resolution was examined (Table 3). The time to DKA resolution was significantly longer among patients with respiratory distress (p = 0.047), odor of acetone on the breath (p = 0.039), altered consciousness (p= 0.006), and severe coma (p = 0.018). Although the time to DKA resolution was longer among patients who were experiencing their first admission for DKA, this difference was not statistically significant (p = 0.725). There was also a significant correlation between the time to DKA resolution and both the PRISM score (r = 0.584, p = 0.002) and the length of stay in the PICU (r = 0.689, p < 0.001).

Laboratory features

Mean laboratory values of the patients were determined as pH = 7.08 ± 0.17, pCO2 = 21.36 ± 8.19 mmHg, HCO3 = 8.72 ± 3.03 mmol/L, lactate = 1.75 ± 1.02 mmol/L, anion gap = 23.69 ± 5.17 mmol/L, WBC = 17.88 ± 9.53 /mm3 CRP = 0.89 ± 1.98 mg/L, glucose = 544.63 ± 161.24 mg/dL, sodium = 133.11 ± 4.68 mEq/L, corrected sodium = 139.78 ± 4.89 mEq/L, potassium = 4.46 ± 0.70 mEq/L, chloride = 106.37 ± 6.55 mEq/L, blood urea nitrogen = 29.51 ± 11.25 mg/dL, creatinine = 0.89 ± 0.29 mg/dL, calculated serum osmolarity = 319.79 ± 15.28 mOsm/L, HbA1c (%) = 12.31 ± 2.51, blood ketones = 5.62 ± 0.76 mmol/L. Linear regression analysis performed for laboratory features revealed that pH (p = 0.001) and HCO3 levels (p = 0.005) were associated with the time to DKA resolution. In the backward model regression analysis, pH values had an independent significant effect on time to DKA resolution (p = 0.014). Finally, there was a significant negative correlation between time to DKA resolution and both pH (r = −0.616, p = 0.001) and HCO3 levels (r = −0.552, p = 0.005).

Discussion

DKA is an acute, severe, and life-threatening complication of type 1 DM in children. It is important to identify the factors affecting the prognosis and resolution time of comas in these patients in order to predict outcomes. Although many studies examine prognostic factors, very few explore those affecting the time to resolution. The present study, which comprehensively examines the factors affecting resolution time, will contribute

to the literature.

It has been reported that DKA resolution time in children can vary between 16 and 75 hours [6,13,14]. In patients with prolonged time to resolution, the stay in the intensive care unit (ICU) is also prolonged. To shorten this time, associated factors must first be identified and followed by early intervention. In our study, mean DKA resolution time was calculated as 20.2 hours, and the mean ICU hospitalization time was 36.37 hours. It is thought that insulin infusion algorithms may affect DKA resolution time. Younis et al. [15] reported that, compared with paper-based insulin infusion, computer-based insulin infusion resulted in a statistically significant decrease in various outcomes, including time to DKA resolution, time on insulin infusion, and ICU stay. Because we use a paper-based insulin infusion algorithm in our clinic, we did not have the opportunity to discuss this difference.

In a recent pediatric study, DKA was found to be significantly more severe among females, but there was no significant relationship between age or living location and DKA severity [14]. Meanwhile, Valero-Guzmán et al. [6] reported a significant negative correlation between age and DKA resolution time. In most studies, DKA resolution time was longer in newly diagnosed patients [6,16]. In our work, similar to Razavi et al. [14], there was no relationship between age or living location and DKA resolution time. Similar to previous studies, we found DKA resolution time to be significantly longer in patients with newly diagnosed DM. Although DKA resolution time was found to be longer among females in our study, the difference was not significant. Although it is not mentioned in other studies, we found DKA resolution time to be significantly longer in patients with a family history of DM.

It is predicted that some clinical characteristics of patients may change DKA episode severity and resolution time. Valero-Guzmán et al. [16] found that DKA resolution time increased significantly as the severity of the disease increased and the duration of symptoms at home lengthened. When they included in the multivariate analysis all variables that were significantly associated in the bivariate analysis, the authors found that, in the most severe DKA episodes, patients who received a larger volume of intravenous fluids with higher NaCl content, took longer to resolve. Baalaajı et al. [17] reported that time to resolution of DKA was significantly longer among patients with acute kidney injury (AKI) than among those without. Since none of our patients had AKI, the effect of this on the time to resolution could not be evaluated. Similar to previous studies, the time to resolution of severe episodes was found to be significantly longer in our study. Although not mentioned in previous research, we examined the relationship between complaints and physical examination findings and DKA resolution time. The time to resolution was found to be significantly longer in patients with respiratory distress, confusion, and a mouth smelling of acetone. In addition, the resolution time was longer in patients presenting with the first DKA attack (compared to the second or third), but the differences were not significant.

In a limited number of adult and pediatric studies, it has been shown that some laboratory values at the time of admission affect DKA episode severity and resolution time. Valero-Guzmán et al. [6] found that there was a significant negative correlation between pH, pCO2, and HCO3 levels at the time of admission and resolution time. In addition, they showed that the pH value at admission had an independent and significant effect on resolution time in their patients. Lee et al. [11] showed, in adult DKA patients, that a lower admission pH and a higher admission serum potassium level were both independent predictors of prolonged time to resolution of DKA. Similarly, in our study, a significant negative correlation was found between pH and HCO3 levels at the time of admission and resolution time. However, no significant correlation was observed between serum electrolytes and other biochemical tests and resolution time. In our study, pH value at admission had an independent effect on resolution time.

Study Limitations and Strength

Our study has several limitations. The main limitation of this study is that it is a retrospective single-center study. We had to exclude three medical records due to incomplete data, and the relatively small sample size limits the study's statistical power.

Conclusion

The results of our study revealed that many factors are effective on resolution time. Although some risk factors prolonged the resolution time, this effect was not significant. Our findings show that the prognosis will be worse and time to resolution will be longer among children with altered consciousness, newly diagnosed DM, respiratory distress, high PRISM score, severe DKA coma, and severe acidosis at the time of admission. Also, pH value had an independent significant effect on time to DKA resolution.

Acknowledgment

The authors would like to thank the Head of the Department of Pediatrics, XXXX Medical Faculty for the assistance during this research.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Mehmet Öztekin, Capan Konca, Mehmet Tekin, Semih Bolu. *Evaluation of factors associated with time to diabetic ketoacidosis resolution in children. Ann Clin Anal Med 2022; DOI: 10.4328/ACAM.21164*