J Pediatr Res 2024;11(2):103-9
DOI: 10.4274/jpr.galenos.2024.15932

Original Article

Pediatric Diabetic Ketoacidosis: A Retrospective Study on Triggering Factors and Complications in a Turkish Intensive Care Unit

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ABSTRACT

Aim: Diabetic ketoacidosis (DKA) is a critical, potentially life-threatening complication of diabetes mellitus (DM) in children, characterized by hyperglycemia, acidosis, and ketonemia/ketonuria. Despite its known risk factors and mortality rates, few studies have focused on the pediatric population, especially in specific regions under standard treatment protocols. This study investigated the demographic, clinical, and laboratory characteristics of children with DKA, identified its triggering factors, the factors affecting DKA severity and its complications, as well as evaluating the outcomes of a standardized treatment protocol in a Turkish pediatric intensive care unit (PICU).

Materials and Methods: In this single-center retrospective study at Göztepe Prof. Dr. Süleyman Yalçın City Hospital's PICU, we included 115 children diagnosed with DKA between 2015 and 2022, following the DKA Treatment Protocol of the Turkish Society of Pediatric Emergency and Intensive Care Medicine and the International Society for Pediatric and Adolescent Diabetes guidelines. We analyzed the patients' demographic, clinical, and laboratory characteristics, treatment outcomes, and their complications using SPSS 25.0.

Results: The sample primarily consisted of female patients and those newly diagnosed with DM, with a median age of 110 months. The mortality rate was low at 0.87%, with one death due to sepsis-induced multiple organ failure. DKA severity (lower GCS, younger age, electrolyte imbalance, acidosis, complications) correlated with longer PICU stays and recoveries in the children. The findings also highlighted the standardized treatment protocol's effectiveness in managing DKA and reducing complications.

Conclusion: This study underscores the importance of early diagnosis, standardized treatment protocols, and comprehensive care in pediatric DKA management. It emphasizes the need for ongoing education and awareness among healthcare providers and caregivers in order to prevent DKA and its severe outcomes. Further multicenter studies are necessary to extend these findings to the broader pediatric population and refine DKA management strategies.

Keywords: Diabetic ketoacidosis, pediatrics, intensive care, treatment outcomes, Turkey

Introduction

Diabetic ketoacidosis (DKA), characterized by hyperglycemia, acidosis, and ketonemia/ketonuria, is a severe acute complication of diabetes mellitus (DM) and a significant cause of morbidity and mortality. DKA occurs in 15-70% of children with DM at disease onset and in 1-10% of those children previously diagnosed with DM (1).

DKA is associated with various clinical signs and symptoms, including dehydration, tachypnea, nausea, vomiting, abdominal pain, and impaired consciousness.

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Received: 19.02.2024 **Accepted:** 30.05.2024

DKA primarily affects children with type 1 DM (T1DM), but children with type 2 DM may also develop DKA (2). In our pediatric intensive care unit (PICU), the DKA Treatment Protocol of the Turkish Society of Pediatric Emergency and Intensive Care Medicine and the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines are followed in the diagnosis, follow-up, and treatment of patients with DKA.

The most well-known conditions which increase the risk of DKA development are reportedly low socio-economic level, discontinuation of insulin use, insulin pump malfunctions, poor metabolic control, infections, adolescence, and difficulty in accessing healthcare services (3).

The mortality rate in children with DKA has been reported as 0.4-3.4% in the literature (4,5). The most common cause of death from acute complications in children with DKA is cerebral edema, followed by electrolyte abnormalities, acute kidney injury (AKI), and pancreatitis (6).

In light of this information, this study was carried out to investigate the demographic, clinical, and laboratory characteristics of those children hospitalized with a diagnosis of DKA in a PICU, the triggering factors of DKA, the factors affecting the severity of DKA and DKA-related complications in order to determine changes which may improve disease outcomes when implemented within the scope of the general management of DKA.

Materials and Methods

This study was designed as a single-center retrospective study. The study protocol was approved by the İstanbul Medeniyet University Göztepe Süleyman Yalçın City Hospital Clinical Research Ethics Committee (approval no: 2022/0666, date: 23.11.2022). This study was conducted in accordance with the Declaration of Helsinki, good clinical practice, and all applicable laws and regulations.

The study population consisted of 2,460 children monitored in the PICU of Göztepe Süleyman Yalçın City Hospital, which has a capacity of 9 beds and serves approximately 250 teritary pediatric (6 months to 18 year old) intensive care patients per year. It was carried out between January 2015 and December 2022. The patients' data were obtained from the archive files available in the hospital information management system. Children with incomplete information in their files, those with only hyperglycemia, and those who did not meet the diagnostic criteria for DKA were excluded from this study. In total, our study included 115 children hospitalized with DKA in our PICU, representing 4.7% of all patients admitted during the study period.

DKA Treatment Protocol of the Turkish Society of Pediatric Emergency and Intensive Care Medicine and ISPAD guidelines were used in diagnosing DKA, determining its severity, and classifying the patients (1,3).

The anamneses of the patients were evaluated in order to determine whether they were newly diagnosed with DM, whether they had previously had DKA, and how many DKAs they had had. In this context, the patients' ages, genders, body mass index values, admission dates to the PICU, admission symptoms, Glasgow Coma Scale scores, mechanical ventilation needs, duration of crystallized insulin intakes, lengths of PICU and hospital stays and mortality status were recorded. Serum biochemistry measurements included the measurement of serum glucose, sodium, blood urea nitrogen, creatinine, blood and urine ketone and hemoglobin A1c (HbA1c) values, as well as pH, bicarbonate (HCO_3^-), carbon dioxide (CO_2) and lactate levels within the scope of venous blood gas analysis. The data recorded on a data form also included whether the patients had experienced cerebral edema, AKI, infection, etc., during their treatment. AKI cases were defined in accordance with the Kidney Disease: Improving Global Outcomes clinical practice guidelines. Accordingly, those children with an increase in serum creatinine levels of at least 1.5 times compared to their estimated baseline values were considered to have AKI (7).

Statistical Analysis

The collected data were analyzed using the SPSS 25.0 (Statistical Product and Service Solutions for Windows, Version 25.0, IBM Corp., Armonk, NY, US, 2017) software package. The study's findings are presented as means and standard deviations (SD) or frequencies and percentages. The Kolmogorov-Smirnov test was used to determine whether numerical variables conformed to the normal distribution. One-way analysis of variance (ANOVA), an extension of the independent samples t-test, was used to compare data meeting parametric assumptions. The Mann-Whitney U test was used to analyze relationships between skewed variables, and Pearson's correlation analysis was used to analyze the relationships between numerical variables. Values of $p \leq 0.05$ were deemed to indicate statistical significance.

Results

The incidence of DKA among all patients followed up at our institution has ranged from 1.9% to 11% over the

years. Our study of DKA patients found a predominance of newly diagnosed and females with a median age of 110 [interquartile range (IQR), 56-165] months. Almost all of the patients had T1DM (96.5%). On the other hand, most of the patients did not have any comorbidity or a history of DKA attacks (62.6%). Analysis of our cohort revealed a recurrent DKA rate of 18.2%.

There was no mortality except for one patient who presented with DKA and sepsis and died due to sepsis-driven multiple organ failure and brain edema. The median duration of DM in those patients with a diagnosis of DM was 5 (IQR, 3.5-8) years, and the median HbA1c level was 12.3% (IQR, 11%-14.4%). The patients' demographic characteristics and admission findings are given in Table I.

Accordingly, among those patients hospitalized with a diagnosis of DKA, patients newly diagnosed with DM were significantly younger than those previously diagnosed with DM (p=0.00, <0.001). The pediatric risk of mortality III scores and HbA1c values were found to be significantly higher in those patients with newly diagnosed DM than in those with previously diagnosed DM (p≤0.05). On the other hand, there was no significant difference in the time to recovery from DKA between those patients with newly diagnosed DM and those with previously diagnosed DM.

Table I. Patients' demographic characteristics and admission findings

Variables	Overall study group (n=115)	Patients newly diagnosed with DM (n=36)	Patients previously diagnosed with DM (n=79)	p values
Age (months), median (IQR)	110 (56-165)	164 (122-184)	88 (39-132)	**<0.001**
Male gender, n (%)	43 (37.4)	8 (22)	35 (44.3)	0.037
PRISM III score, median (IQR)	4 (2.5-5.8)	3.6 (1.5-4.9)	4.6 (2.8-6.9)	**0.010**
GCS score, median (IQR)	14 (13-15)	14 (13-14)	14 (12-15)	**0.046**
DM diagnosis, n (%)				
Previously diagnosed	36 (31.3)	-	-	-
Newly diagnosed	79 (68.7)	-	-	-
Type of DM, n (%)				
Type 1	109 (96.5)	32 (88)	79 (100)	0.014
Type 2	2 (1.8)	2 (6)	0	0.014
MODY	2 (1.8)	2 (6)	0	0.014
Patients with a comorbidity, n (%)	17 (14.8)	4 (11.1)	13 (16.5)	0.570
DKA severity, n (%)				
Severe DKA	102 (88.7)	29 (81)	73 (92.4)	0.064
Moderate DKA	13 (11.3)	7 (19)	6 (7.6)	
DKA history, n (%)				
None	94 (81.7)	15 (41.6)	79 (100)	<0.001
Second DKA	12 (10.4)	12 (33.3)	0 (0)	
Third DKA or more	9 (7.8)	9 (25)	0 (0)	
Mortality rate, n (%)	1 (0.9)	0	1 (1.26)	
Duration of DM in previously diagnosed patients, median (IQR)		5 (3.5-8)		
Admission findings, n (%)				
Polydipsia	56 (48.7)	3 (8.3)	53 (67.1)	**<0.001**
Polyuria	59 (51.3)	4 (11.1)	55 (69.6)	**<0.001**
Tachypnea	39 (33.9)	17 (47.2)	22 (27.8)	**0.042**
Weight loss	26 (22.6)	0 (0)	26 (32.9)	**<0.001**

Table I. Continued

Variables	Overall study group (n=115)	Patients newly diagnosed with DM (n=36)	Patients previously diagnosed with DM (n=79)	p values
Enuresis	6 (5.2)	0 (0)	6 (7.6)	0.090
Nausea and vomiting	70 (60.9)	25 (69.4)	45 (56.9)	0.220
Stomach ache	30 (26.1)	9 (25)	21 (26.5)	0.850
Fatigue	72 (62.6)	17 (19.4)	55 (69.6)	**0.020**
Laboratory parameters, median (IQR)				
HbA1c level (%)	12.3 (11-14.4)	10.8 (8.8-11.2)	13.6 (12.7-14.8)	**<0.001**
pH value	6.9 (6.9-7)	6.8 (6.8-6.9)	6.96 (6.9-7.0)	**<0.001**
Bicarbonate level (mmol/L)	7.8 (5.8-6.9)	4.75 (3.6-5.8)	6 (5.1-7.2)	**<0.001**
Lactate level (mmol/L)	1.55 (1.1-2.4)	1.4 (0.9-2)	1.6 (1.1-2.7)	0.120
Glucose level (mg/dL)	474 (405-597)	490.5 (442-574)	468 (379-599)	0.340
Blood ketone level (mmol/L)	5.8 (4.1-7.7)	6.7 (4.7-8)	5.3 (4-7)	0.150
Urea level (mg/dL)	26 (19-36)	28 (20-41)	26 (17.8-36)	0.270
Sodium level (mmol/L)	134 (131-139)	135 (132-141)	134 (131-138)	0.530
Triggering factors, n (%)				
Insulin disruption	20 (17.4)	20 (55.5)	0 (0)	<0.001
Insulin pump malfunctions	2 (1.7)	2 (5.5)	0 (0)	NaN
Pneumonia	10 (8.7)	2 (5.5)	8 (10.1)	0.870
Gastroenteritis	9 (7.8)	5 (13.9)	4 (5)	0.140
Urinary tract infection	7 (6.1)	2 (5.5)	5 (6.3)	0.420

DM: Diabetes mellitus, IQR: Interquartile range, PRISM III: Pediatric risk of mortality III, GCS: Glasgow coma scale, MODY: Maturity-onset diabetes of the young, DKA: Diabetic ketoacidosis, HbA1c: Hemoglobin A1c

The median time to recovery from DKA was 19 (IQR, 13-26.2) hours, the median length of PICU stay was 2 (IQR, 2-3) days, and the median length of hospital stay was 8 (IQR, 5-12) days. The most prevalent complications encountered in our study were cerebral edema (6.9%) and AKI (6%).

In our cohort, DKA discharge time was significantly shorter with increasing GKS, pH, and bicarbonate levels (p=0.000, p=0.003, p=0.012, respectively). Hypernatremia, the need for invasive mechanical ventilation, the need for dialysis, cerebral edema, AKI, and older age were significantly associated with longer DKA discharge times (p=0.022, p=0.000, p=0.001, p=0.017, p=0.000, p=0.015, respectively). PICU length of stay was significantly shorter with increasing GKS and pH levels (p=0.000, p=0.007, respectively). Age, urea levels, sodium levels, the need for invasive mechanical ventilation, the need for dialysis, AKI, cerebral edema, and MODS were positively correlated with PICU lengths of stay (p=0.009, p=0.021, p=0.001, p=0.000, p=0.000, p=0.000, p=0.006, p=0.011, respectively) (Table II).

Table II. Factors affecting time to recovery from DKA and length of PICU stay

	Time to recovery from DKA		Length of PICU stay	
	r	p values	r	p values
GCS score	-0.374	<0.001	-0.356	**<0.001**
PRISM III score	0.033	0.725	-0.184	0.050
Age	0.230	**0.015**	0.243	0.009
HbA1c level	-0.024	0.830	0.074	0.525
Glucose level	-0.074	0.430	0.030	0.752
Urea level	0.163	0.085	0.220	**0.021**
Sodium level	0.215	**0.022**	0.290	**0.001**
DM diagnosis	-0.112	0.237	0.061	0.521
DKA severity	0.151	0.108	0.184	**0.049**
Duration of DM	0.131	0.164	-0.023	0.805
DKA history	0.120	0.205	-0.143	0.128
pH value	-0.280	**0.003**	-0.251	**0.007**
Bicarbonate level	-0.238	**0.012**	-0.128	0.181
Lactate level	-0.087	0.417	-0.199	0.060

Table II. Continued

	Time to recovery from DKA		Length of PICU stay	
	r	**p values**	**r**	**p values**
Base deficit	-0.151	0.108	-0.042	0.654
Blood ketone level	-0.120	0.418	0.028	0.848
IMV need	0.404	**<0.001**	0.429	**<0.001**
Dialysis need	0.307	**0.001**	0.328	**<0.001**
Complications	0.399	**<0.001**	0.398	**<0.001**
Brain edema	0.223	**0.017**	0.256	**0.006**
Hypokalemia	0.297	**0.001**	0.322	**<0.001**
AKI	0.357	**<0.001**	0.257	**0.006**
MODS	0.177	0.060	0.237	**0.011**

DKA: Diabetic ketoacidosis, PICU: Pediatric intensive care unit, GCS: Glasgow coma scale, PRISM III: Pediatric risk of mortality III, HbA1c: Hemoglobin A1c, IMV: Invasive mechanical ventilation, AKI: Acute kidney injury, MODS: Multiple organ dysfunction syndrome

Discussion

Our study aimed to contribute to the literature by characterizing the demographic, clinical, laboratory, precipitating factors, and complication profiles of cases followed up in a PICU due to DKA. However, it was not possible to reach significant findings on those factors which determine the severity of DKA. Therefore, there is a need for prospective studies with larger sample sizes.

The proportion of DKA cases among patients admitted during the study period was consistent with the range of 0.8% to 5.6% reported in a meta-analysis of 19 studies involving adult patients from North America, Europe, and Israel (8). Similarly, a study by Albuali and Al-Qahtani (9) reported a DKA incidence of 3.93% in critically ill pediatric patients.

In a review of our PICU population, the incidence of DKA did not demonstrate a statistically significant trend over time. In contrast, a significant increase in the incidence of DKA in 2020 and 2021 due to the coronavirus disease-2019 (COVID-19) pandemic was reported in the literature (10). The discrepancy between the said finding of our study and the relevant findings of studies in the literature can be attributed to the fact that the emergency and outpatient services in our country continued to operate effectively during the COVID-19 pandemic.

In our study, 68.7% of the patients hospitalized in the PICU due to DKA did not have a history of T1DM. This finding is consistent with other relevant studies conducted in other developing countries (11). The overall mortality rate in children with DKA reportedly varies between 3.4-13.4% in developing countries (12). In comparison, only one of the 115 DKA patients in our sample died. The cause of death of the said patient was sepsis-related multiple organ failure. In addition, the patient also developed cerebral edema during the follow-up period, but this was treated successfully. In undiagnosed diabetic patients, stress factors such as intercurrent infections pave the way for a worsening of the clinical condition and a deterioration of the response to treatment.

The use of bicarbonate to eliminate acidosis in children with DKA is not recommended unless there is life-threatening hyperkalemia associated with an increased risk of complications such as cerebral edema and hypokalemia (1). In accordance with this, bicarbonate was not used in any patient in our cohort. Insulin treatment generally causes a decrease in the serum potassium level due to an increase in potassium uptake into the cell and potentially causes insulin to have an aldosterone-like effect on the renal tubule, further increasing potassium losses through urine (13).

However, severe hypokalemia (<2 mEq/L) has been reported very rarely in children with DKA in the literature (14). In parallel, severe hypokalemia was not observed in any patient in our cohort. Additionally, T-wave flattening, QT prolongation, short P-R interval, U wave, ventricular dysrhythmia, and electrocardiographic changes were not observed in patients with hypokalemia (15).

AKI is one of the most common complications of severe DKA and it is often associated with reduced renal perfusion caused by intravascular volume depletion (16). Consistent with the relevant data in the literature, AKI was detected in 6% of those patients with DKA admitted to the PICU in our cohort (17,18). The mechanism of brain edema, which is the leading cause of mortality among DKA complications, is thought to be cerebral hypoperfusion and reperfusion injury associated with neuroinflammation (19). In our investigation, cerebral edema exhibited a higher incidence than the previously reported rate of 1% in the medical literature (20). Our finding might be attributed to the fact that 88.7% of DKA patients admitted to our clinic had severe DKA. In the literature, the overall mortality rate in pediatric patients with DKA who develop brain edema has been reported to be around 20% (21,22). In comparison, in our study, one (16.7%) of the six patients with brain edema died due to sepsis-related multi-organ failure. None of the patients with DKA who we followed up with brain edema had neurological sequelae at the time of discharge, and all of them were successfully treated with mannitol, a hypertonic agent. Consistent with the published literature,

our study identified the most frequent causes of recurrent DKA to be accidental/deliberate insulin discontinuation, intercurrent infections, and undetected malfunctions of insulin pumps (1). The involvement of clinical psychologists and appropriate therapeutic interventions are paramount in mitigating these detrimental factors.

The primary strength of our study was that the data of the patients who were followed up and treated under the same protocol and hospitalized for a certain period were analyzed without exceptions which could have created bias, thus making our findings fully comparable. Additionally, our sample size was large enough to include patients of all pediatric ages who were hospitalized for a relatively common reason. We could not find any other comparable study conducted in Turkey recently.

Study Limitations

The primary limitations of our study were its retrospective nature, reliance on archival records, and difficulty establishing causality. The lack of sociodemographic data, such as parental education and the parents' roles in their children's compliance with glycemic control, which may be influential in developing DKA in the pediatric population, may be considered another limitation. Future large-scale, multicenter, and well-designed prospective studies may shed more light on DKA's prevalence, complications, and importance in this special patient population.

Conclusion

This study, conducted in a PICU in Turkey, provides valuable insights into the demographic, clinical, and laboratory characteristics of those children diagnosed with DKA, alongside evaluating the triggering factors, severity, complications, and outcomes under a standardized treatment protocol. Our findings highlight the predominance of female patients and a significant portion of newly diagnosed DM cases within the study population. The low mortality rate observed, at 0.87%, underscores the effectiveness of the standardized treatment protocols in place, which align with the guidelines of the Turkish Society of Pediatric Emergency and Intensive Care Medicine and the ISPAD.

The association between the severity of DKA at admission, the presence of complications such as cerebral edema or AKI, and the length of PICU stay with recovery time emphasizes the critical need for early diagnosis and the initiation of standardized treatment protocols. These findings advocate for the importance of continuous education and awareness among healthcare providers and caregivers in order to prevent the occurrence of DKA and its severe outcomes.

Moreover, this study sheds light on the necessity for further multicenter studies in order to generalize these findings to the broader pediatric population across different regions. Such research could lead to the development of more refined DKA management strategies, potentially reducing the incidence and severity of DKA in children. Our research underscores the critical role of standardized care protocols in managing pediatric DKA effectively and highlights areas for future investigation in order to further enhance patient outcomes.

Acknowledgment

The authors would like to convey their utmost gratitude to their colleagues in Göztepe Prof. Dr. Süleyman Yalçın City Hospital and DRK-Nordsee-Reha-Klinik and the study participants for their contributions to this study.

Ethics

Ethics Committee Approval: The study protocol was approved by the İstanbul Medeniyet University Göztepe Süleyman Yalçın City Hospital Clinical Research Ethics Committee (approval no: 2022/0666, date: 23.11.2022).

Informed Consent: This study was designed as a single-center retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.Ş.D., M.E., M.D., Concept: A.A., Design: A.A., Data Collection and/or Processing: A.A., A.Ş.D., M.E., Analysis and/or Interpretation: A.A., A.Ş.D., M.D., Literature Search: A.A., Writing: A.A.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

Financial Disclosure: The authors disclose that this research study was not funded by any specific grants from public, commercial, or not-for-profit sectors.

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