ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Comprehensive Assessment of the Characteristics of Pediatric Patients with Diabetic Ketoacidosis: 11 Years of Data from a Tertiary Center

Diyabetik Ketoasidozlu Pediatrik Hastaların Özelliklerinin Kapsamlı Değerlendirmesi: Üçüncü Basamak Bir Merkezden 11 Yıllık Veri

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Abstract

Introduction: Our objective is to describe comprehensive patient characteristics and explore their relationships with the presence and severity of diabetic ketoacidosis (DKA) in pediatric patients with diabetes mellitus (DM).

Materials and Methods: This retrospective, single-center study included pediatric patients with DM. Patients were categorized into those with and without DKA, and those with DKA were subclassified into mild, moderate, and severe groups. Clinical symptoms, biochemical parameters, and treatment needs, including intensive care unit (ICU) requirements, were evaluated. Data were obtained from electronic medical records, and analyses involved comparisons between patients with and without DKA and between DKA severity groups.

Results: The study included 180 admissions of 150 patients, with 84 (46.7%) involving DKA. Compared to non-DKA subjects, patients with DKA had higher frequencies of abdominal pain (p=0.048), fatigue (p=0.011), vomiting (p<0.001), nausea (p=0.021), lethargy (p=0.046), and tachypnea (p=0.006), as well as higher prevalence of prior DKA (p<0.001), active infection (p=0.011), type 1 DM (p=0.015), and ICU admission (p=0.020). DKA patients had higher blood glucose (p<0.001), creatinine (p=0.009), and leukocyte counts (p<0.001), while sodium (p=0.045) and potassium (p=0.018) were lower. Patients with severe DKA had higher leukocyte count (p=0.001) compared to those with mild and moderate DKA, with a longer duration of ketoacidosis (p<0.001) and more frequent ICU admission (p=0.020). According to logistic regression analysis results, vomiting (p<0.001) and previous DKA history (p<0.001) were independent risk factors for DKA. For severe DKA, fatigue (p=0.031) was an independent risk factor.

Conclusion: This study presents a comprehensive dataset concerning pediatric patients with DKA, and identifies multiple factors associated with DKA and its severity.

Keywords
Diabetic ketoacidosis, type 1 diabetes mellitus, pediatrics, metabolic disturbances, intensive care units

Anahtar kelimeler
Diyabetik ketoasidoz, tip 1 diabetes mellitus, pediatri, metabolik bozukluklar, yoğun bakım üniteleri

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Öz

Giriş: Diyabet mellituslu (DM) pediatrik hastalarda diyabetik ketoasidozun (DKA) varlığı ve şiddeti ile ilişkili kapsamlı hasta özelliklerini tanımlamayı amaçladık.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya DM'li pediatrik hastalar dahil edildi. Hastalar DKA'lı ve DKA'sız olarak kategorize edildi ve DKA'lı hastalar hafif, orta ve şiddetli olarak alt gruplara ayrıldı. Klinik semptomlar, biyokimyasal

parametreler ve yoğun bakım ünitesi (YBÜ) ihtiyacı dahil tedavi gereksinimleri değerlendirildi. Veriler elektronik tıbbi kayıtlardan elde edildi ve analizler DKA'lı ve DKA'sız hastalar ile DKA şiddet grupları arasındaki karşılaştırmaları içerdi.
Bulgular: Çalışmaya 150 hastanın 180 başvurusu dahil edildi ve bunların 84'ü (%46,7) DKA ile ilişkiliydi. DKA'sız hastalara kıyasla, DKA'lı hastalarda karın ağrısı (p=0,048), yorgunluk (p=0,011), kusma (p<0,001), bulantı (p=0,021), letarji (p=0,046) ve taşipne (p=0,006) sıklığı daha yüksekti. Ayrıca, önceki DKA öyküsü (p<0,001), aktif enfeksiyon (p=0,011), tip 1 DM (p=0,015) ve YBÜ yatışı (p=0,020) daha yaygındı. DKA'lı hastalarda kan şekeri (p<0,001), kreatinin (p=0,009) ve lökosit sayısı (p<0,001) daha yüksekken, sodyum (p=0,045) ve potasyum (p=0,018) daha düşüktü. Şiddetli DKA'lı hastalarda, hafif ve orta DKA'lı hastalara kıyasla daha yüksek lökosit sayısı (p=0,001) seviyeleri vardı. Ayrıca, ketoasidoz süresi daha uzun (p<0,001) ve YBÜ yatışı daha sıktı (p=0,020). Lojistik regresyon analizi sonuçlarına göre, kusma (p<0.001) ve önceki DKA geçmişi (p<0.001) DKA için bağımsız risk faktörleriydi. Şiddetli DKA için ise yorgunluk (p=0.031) bağımsız bir risk faktörüydü.
Sonuç: Bu çalışma, DKA'lı pediatrik hastalarla ilgili kapsamlı bir veri seti sunmakta ve DKA ile şiddetiyle ilişkili çok sayıda faktörü tanımlamaktadır.

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases in childhood, and the increasing global incidence is a cause for concern (1,2). Data from international organizations indicate that the prevalence of type 1 DM in the pediatric population is rising rapidly (1-3). The management of pediatric DM is critical not only for improving patients' quality of life but also for preventing adverse outcomes and the development of long-term complications.

Diabetic ketoacidosis (DKA) is a common acute and potentially life-threatening complication resulting from insulin deficiency or increased insulin requirements in individuals with diabetes (4). This manifestation is characterized by hyperglycemia, ketonemia, and metabolic acidosis and is particularly common in children newly diagnosed with type 1 DM (5). Delayed diagnosis can lead to severe consequences such as cerebral edema, shock, multiorgan failure, and death (6). Early recognition and prompt treatment are essential to reduce morbidity and mortality, especially in severe cases. DKA severity is classified into mild, moderate, and severe, which directly affect clinical management and patient prognosis (7). Severe DKA is associated not only with challenging treatments but also with an increased risk of complications (7,8).

Despite known associations between DKA and factors like delayed diagnosis or infections, limited pediatric-specific data exist on which demographic, clinical, and laboratory factors independently predict DKA severity. Better definition of clinical and laboratory markers associated with DKA severity will contribute to optimizing both preventive approaches and treatment algorithms. Furthermore, collection of comprehensive data including maternal/paternal characteristics, natal properties, expanded symptomatology, anthropomorphic features, disease histories, autoantibody profiles, and a battery of relevant laboratory measurements has the potential to provide crucial information regarding DKA in the pediatric age.

In line with this, our hypothesis is that there are significant relationships between the development and severity of DKA and the demographic, clinical, and laboratory factors in pediatric patients. Therefore, we sought to identify factors associated with the presence of DKA in children with DM and to determine independent markers that may predict the severity of DKA and other patient characteristics.

Materials and Methods

Ethics, Study Design and Population

The study received ethical approval from the Bakırköy Dr. Sadi Konuk Training and Research Ethics Committee (date: 15.05.2017, approval number: 2017-03-20). All procedures were conducted in compliance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration, including its subsequent amendments. This retrospective study includes patients hospitalized for diagnosis and treatment of DM at the Department of Pediatrics and the Pediatric Intensive Care Unit of our hospital, between January 2006 and March 2017. Patients aged 18 years and older, as well as patients with missing data, were excluded from the study. Since some patients had multiple admissions, each admission was considered as a separate case.

Data Collection

All data were retrospectively obtained by reviewing hospital records that coincided with the index admission of each specific case. The study collected data on the following variables at the time of admission: patient age, sex, anthropometric measurements (height, weight, and body mass index), predominant presenting symptom,

time between symptom onset and hospital admission, consanguinity status, gestational age at birth, parental education status, gestational diabetes during pregnancy, family history of diabetes, type of delivery (vaginal or cesarean), birth weight, history of surgery, comorbidities, laboratory findings (detailed below), previous history of DKA, insulin treatment dose, active infection status and type at the time of admission, type of diabetes [Type 1 DM, Type 2 DM, or Maturity-Onset Diabetes of the Young (MODY)], Tanner stage, length of hospital stay, stay in the intensive care unit (ICU), and diagnosis status (newly diagnosed or previously diagnosed).

The admission of patients to the ICU was based on the standard protocols of our clinic and the criteria defined in the existing literature (9,10). Indications for ICU admission included severe metabolic disturbances, significant acidosis (pH <7.1), severe electrolyte imbalances, hypotension, altered consciousness (lethargy, stupor, or coma), severe dehydration (≥10% fluid loss), signs of shock, and suspected cerebral edema. Patients meeting these criteria were evaluated for close monitoring and advanced supportive treatment in the ICU.

Type 1 DM, Type 2 DM, and MODY diagnoses were made according to the current American Diabetes Association (ADA) criteria. Tanner staging was performed as previously described (11).

DKA was defined as hyperglycemia with a venous blood pH of less than 7.3 or a bicarbonate level below 15 mEq/dL. The severity of DKA was classified based on venous blood pH as follows: severe if pH was less than 7.1, moderate if pH was between 7.1 and 7.2, and mild if pH was between 7.2 and 7.3 (7).

Laboratory Analysis

Laboratory analyses were conducted at the certified biochemistry laboratory of our hospital following internationally recognized technical standards. The following parameters, measured from the blood samples taken at the time of admission, were included in the study: blood fasting glucose, insulin, C-peptide, HbA1c, sodium, potassium, urea, creatinine, C-reactive protein, white blood cell (WBC) count, glucose and ketones in urine, islet autoantibodies, insulin autoantibodies, anti-glutamic acid decarboxylase, transglutaminase IgA, anti-gliadin IgA, anti-thyroglobulin, anti-thyroid peroxidase, endomysium IgA, and arterial blood pH, HCO_3, and pCO_2.

Statistical Analysis

Data were collected into a spreadsheet and then transferred to an SPSS dataset for analyses (SPSS version 25; IBM Corp., Armonk, NY, USA). In all statistical tests, a p value of <0.05 was considered significant. The normality of quantitative data was assessed by examining histograms and Q-Q plots. Descriptive statistics were summarized with mean ± standard deviation or median (25-75th percentile), depending on normal or non-normal distributions, respectively. For categorical variables, frequency (percentage) values were used. Between-group comparisons of normally distributed continuous variables were performed using the Student's t-test or one-way analysis of variance (ANOVA), depending on the number of groups. Between-group comparisons of non-normally distributed continuous variables were performed using the Mann-Whitney U test or Kruskal-Wallis test, depending on the number of groups. Between-group comparisons of categorical variables were performed using appropriate chi-square tests or the Fisher's exact test (or its Freeman-Halton extension). Follow-up data were analyzed using repeated measures ANOVA or Friedman's ANOVA by ranks, depending on distribution characteristics. Pairwise adjustments for multiple comparisons were done with the Bonferroni correction. Multivariable logistic regression analysis (forward conditional selection method) was performed to determine independent risk factors of the development and severity of DKA. Statistically significant variables according to univariate analysis results were included to regression analysis.

Results

A total of 180 admissions from 150 patients were included in the study. Each admission was accepted as a separate case for the purpose of all analyses. At the time of admission, DKA was present 84 cases (46.7%; all type 1 DM), while 96 patients were non-DKA (53.3%; 91.67% type 1 DM). There were no significant differences in age (p=0.840) and sex (p=0.106) between patients with and without DKA. The median time between symptom onset and hospital admission was significantly shorter in patients with DKA. The percentage of patients presenting with abdominal pain (p=0.048), fatigue (p=0.011), vomiting (p<0.001), nausea (p=0.021), lethargy (p=0.046), and tachypnea (p=0.006) was significantly higher in those with DKA (Table 1).

The percentage of patients with a previous history of DKA (p<0.001), type 1 DM (p=0.015), and those requiring ICU care (p=0.020) was significantly higher in the DKA group (Table 2). No patient mortality was recorded during follow-up.

Table 1. Demographics and clinical variables with regard to diabetic ketoacidosis presence				
		Diabetic ketoacidosis		
	Total (n=180)	Absent (n=96)	Present (n=84)	p-value
Age, years (n=180)	10 (6-12.5)	9 (6-13)	10.5 (6-12)	0.840‡
Sex (n=180)				
Girl	87 (48.33%)	41 (42.71%)	46 (54.76%)	0.106§
Boy	93 (51.67%)	55 (57.29%)	38 (45.24%)	
Height, cm (n=118)	136.57±23.19	138.43±22.00	134.04±24.72	0.312†
Weight, kg (n=145)	34 (25-47)	35 (25-50.5)	33 (21-42)	0.171‡
Body mass index, kg/m^2 (n=118)	17.31 (15.26-19.86)	17.46 (15.32-21.29)	17.06 (14.85-19.22)	0.238‡
Time between symptoms and admission, days (n=139)	10 (3-30)	15 (7-45)	7 (2-15)	**<0.001‡**
Symptoms/Findings (n=180)				
Polydipsia	80 (44.44%)	46 (47.92%)	34 (40.48%)	0.316§
Polyuria	73 (40.56%)	44 (45.83%)	29 (34.52%)	0.123§
Abdominal pain	20 (11.11%)	6 (6.25%)	14 (16.67%)	**0.048§**
Fatigue	18 (10.00%)	4 (4.17%)	14 (16.67%)	**0.011§**
Dryness of the mouth	5 (2.78%)	2 (2.08%)	3 (3.57%)	0.665#
Weight loss	23 (12.78%)	11 (11.46%)	12 (14.29%)	0.732§
Vomiting	32 (17.78%)	3 (3.13%)	29 (34.52%)	**<0.001§**
Headache	5 (2.78%)	3 (3.13%)	2 (2.38%)	1.000#
Enuresis	13 (7.22%)	9 (9.38%)	4 (4.76%)	0.366§
Nausea	5 (2.78%)	0 (0.00%)	5 (5.95%)	**0.021#**
Hypoglycemia	2 (1.11%)	1 (1.04%)	1 (1.19%)	1.000#
Lethargy	4 (2.22%)	0 (0.00%)	4 (4.76%)	**0.046#**
Back pain	1 (0.56%)	0 (0.00%)	1 (1.19%)	0.467#
Sweating	1 (0.56%)	0 (0.00%)	1 (1.19%)	0.467#
Halitosis	1 (0.56%)	0 (0.00%)	1 (1.19%)	0.467#
Asthenia	3 (1.67%)	3 (3.13%)	0 (0.00%)	0.249#
Tachypnea	11 (6.11%)	1 (1.04%)	10 (11.90%)	**0.006§**
Polyphagia	2 (1.11%)	2 (2.08%)	0 (0.00%)	0.499#
Genital itching	2 (1.11%)	2 (2.08%)	0 (0.00%)	0.499#
Fever	4 (2.22%)	1 (1.04%)	3 (3.57%)	0.340#
Cough	1 (0.56%)	1 (1.04%)	0 (0.00%)	1.000#
Chest pain	1 (0.56%)	1 (1.04%)	0 (0.00%)	1.000#
Poor general condition	1 (0.56%)	0 (0.00%)	1 (1.19%)	0.467#
Growth retardation	1 (0.56%)	1 (1.04%)	0 (0.00%)	1.000#
Hyperglycemia	12 (6.67%)	10 (10.42%)	2 (2.38%)	0.063§
Dizziness	1 (0.56%)	1 (1.04%)	0 (0.00%)	1.000#

Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables, † Student's t test, ‡ Mann Whitney U test, § chi-square test, # Fisher's exact test, ¶ Fisher-Freeman-Halton test, *Statistically significant category for the variables with three or more categories. Statistically significant p values are shown in bold

Patients with DKA had significantly higher levels of blood glucose (p<0.001), creatinine (p=0.009), and WBC counts (p<0.001) at admission, while levels of C-peptide (p<0.001), sodium (p=0.045) and potassium (p=0.018) were significantly lower (Table 3).

There were no significant differences in age (p=0.170) and sex (p=0.474) in the DKA subgroups comprised of patients with mild, moderate, and severe DKA. In the severe DKA group, the frequency of presenting with fatigue was significantly higher compared to the mild DKA group (p=0.021 (Table 4).

Table 2. Summary of family history and pre- and post-diabetes variables with regard to diabetic ketoacidosis presence

		Diabetic ketoacidosis		
	Total (n=180)	**Absent (n=96)**	**Present (n=84)**	**p-value**
Consanguinity (n=158)	35 (22.15%)	20 (23.53%)	15 (20.55%)	0.797§
Gestational week at birth (n=170)				
Term	159 (93.53%)	82 (92.13%)	77 (95.06%)	0.644§
Preterm	11 (6.47%)	7 (7.87%)	4 (4.94%)	
Gestational diabetes (n=161)	2 (1.24%)	0 (0.00%)	2 (2.67%)	0.215#
Diabetes in family/relatives (n=161)	102 (63.35%)	52 (60.47%)	50 (66.67%)	0.415§
Type 1 diabetes in family/relatives	13 (8.07%)	8 (9.30%)	5 (6.67%)	0.747§
Type 2 diabetes in family/relatives	98 (60.87%)	50 (58.14%)	48 (64.00%)	0.447§
Type of birth (n=170)				
Vaginal birth	97 (57.06%)	50 (55.56%)	47 (58.75%)	0.674§
Cesarean	73 (42.94%)	40 (44.44%)	33 (41.25%)	
Weight at birth, g (n=158)	3294.43±553.08	3224.77±565.04	3377.64±530.39	0.084†
Comorbidity (n=170)	23 (13.53%)	15 (16.67%)	8 (10.00%)	0.297§
Previous diabetic ketoacidosis history (n=180)	84 (46.67%)	16 (16.67%)	68 (80.95%)	**<0.001§**
Diagnosis (n=180)				
Type 1 DM	172 (95.56%)	88 (91.67%)	84 (100.00%)*	**0.015¶**
Type 2 DM	7 (3.89%)	7 (7.29%)	0 (0.00%)*	
MODY	1 (0.56%)	1 (1.04%)	0 (0.00%)	
Tanner stage (n=100)				
Stage 1	62 (62.00%)	32 (57.14%)	30 (68.18%)	0.186¶
Stage 2	6 (6.00%)	6 (10.71%)	0 (0.00%)	
Stage 3	9 (9.00%)	5 (8.93%)	4 (9.09%)	
Stage 4	5 (5.00%)	2 (3.57%)	3 (6.82%)	
Stage 5	18 (18.00%)	11 (19.64%)	7 (15.91%)	
Length of stay in hospital, days (n=147)	8 (5-11)	8 (5-11)	8 (4-12)	0.787‡
Stay in intensive care unit (n=146)	13 (8.90%)	2 (2.74%)	11 (15.07%)	**0.020§**
Active infection (n=180)	18 (10.00%)	4 (4.17%)	14 (16.67%)	**0.011§**
Diagnosis time (n=136)				
Newly diagnosed	80 (58.82%)	43 (65.15%)	37 (52.86%)	0.200§
Previously diagnosed	56 (41.18%)	23 (34.85%)	33 (47.14%)	

MODY: Maturity onset diabetes of the young, DM: Diabetes mellitus, Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile - 75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables, † Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test, ¶ Fisher-Freeman-Halton test, *Statistically significant category for the variables with three or more categories. Statistically significant p values are shown in bold

The duration of ketoacidosis was significantly longer (p<0.001) in the severe DKA group compared to the mild and moderate DKA groups. The percentage of patients requiring ICU admission was significantly higher in the severe DKA group compared to the moderate DKA group (Table 5).

In the severe DKA group, the median WBC count at admission was significantly higher compared to both the mild and moderate DKA groups (p=0.001) (Table 6).

Table 3. Laboratory variables with regard to diabetic ketoacidosis presence

		Diabetic ketoacidosis		
	Total (n=180)	**Absent (n=96)**	**Present (n=84)**	**p-value**
Blood glucose, mg/dL (n=166)	431.72±161.54	388.79±160.35	479.00±150.11	**<0.001**†
Insulin, µU/mL (n=111)	3.25 (2.00-8.28)	3.97 (2.00-9.97)	2.00 (1.48-7.78)	0.070‡
C-peptide, ng/mL (n=128)	0.31 (0.19-0.74)	0.45 (0.27-1.01)	0.20 (0.11-0.34)	**<0.001**‡
HbA1c, % (n=149)	11.79±2.38	11.60±2.44	12.02±2.29	0.278†
Sodium, mEq/L (n=166)	134.15±5.20	134.94±4.58	133.32±5.69	**0.045**†
Potassium, mEq/L (n=164)	4.34±0.70	4.47±0.58	4.21±0.78	**0.018**†
Urea, mg/dL (n=163)	25 (20-31)	25 (20.3-31)	24.45 (18-32)	0.627‡
Creatinine, mg/dL (n=163)	0.57 (0.44-0.77)	0.54 (0.43-0.64)	0.63 (0.47-0.86)	**0.009**‡
Islet autoantibody (n=117)				
Negative	22 (18.80%)	13 (19.70%)	9 (17.65%)	0.966§
Positive	95 (81.20%)	53 (80.30%)	42 (82.35%)	
WBC ($x10^3$) (n=150)	10.00 (7.67-13.90)	8.55 (7.14-10.34)	13.75 (10.00-25.50)	**<0.001**‡
CRP, mg/dL (n=143)	0.30 (0.06-0.61)	0.25 (0.05-0.40)	0.34 (0.06-0.96)	0.112‡
Insulin autoantibodies, IU/mL (n=112)	2.68 (0.40-5.07)	2.68 (0.40-5.09)	2.79 (0.40-5.00)	0.846‡
Anti-GAD, IU/mL (n=118)	21.34 (5-105)	9.7 (5-70)	30.13 (5.35-118)	0.237‡
Transglutaminase IgA (n=66)				
Negative	56 (84.85%)	31 (83.78%)	25 (86.21%)	1.000#
Positive	10 (15.15%)	6 (16.22%)	4 (13.79%)	
Anti-gliadin IgA (n=39)				
Negative	38 (97.44%)	18 (100.00%)	20 (95.24%)	1.000#
Positive	1 (2.56%)	0 (0.00%)	1 (4.76%)	
Anti-Tg (n=53)				
Negative	41 (77.36%)	25 (75.76%)	16 (80.00%)	1.000#
Positive	12 (22.64%)	8 (24.24%)	4 (20.00%)	
Anti-TPO (n=54)				
Negative	38 (70.37%)	23 (67.65%)	15 (75.00%)	0.793§
Positive	16 (29.63%)	11 (32.35%)	5 (25.00%)	
Endomysium IgA (n=56)				
Negative	53 (94.64%)	26 (92.86%)	27 (96.43%)	1.000#
Positive	3 (5.36%)	2 (7.14%)	1 (3.57%)	

Anti-GAD: Anti-glutamic acid decarboxylase, Anti-TPO: Anti-thyroid peroxidase, CRP: C-reactive protein, HbA1c: Hemoglobin A1c, WBC: White blood cell count, Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile - 75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables, † Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test, ¶ Fisher-Freeman-Halton test, *Statistically significant category for the variables with three or more categories. Statistically significant p values are shown in bold

Table 4. Demographics and clinical variables with regard to diabetic ketoacidosis severity				
	Diabetic ketoacidosis severity			
	Mild (n=19)	Moderate (n=28)	Severe (n=37)	p-value
Age, years (n=84)	8 (2 - 12)	11 (7 - 12.5)	11 (8 - 12)	0.170‡
Sex (n=84)				
Girl	9 (47.37%)	14 (50.00%)	23 (62.16%)	0.474§
Boy	10 (52.63%)	14 (50.00%)	14 (37.84%)	
Height, cm (n=50)	118.81±20.60	143.07±18.49*	137.15±27.00	**0.024**†
Weight, kg (n=65)	24 (14 - 31)	37.5 (30.4 - 44.5)*	36 (21 - 44.5)*	**0.012**‡
Body mass index, kg/m^2 (n=50)	16.82 (14.35 - 17.80)	16.57 (15.57 - 19.23)	17.58 (14.42 - 19.86)	0.638‡
Time between symptoms and admission, days (n=72)	8.5 (2 - 17)	7 (3 - 15)	3 (2 - 15)	0.790‡
Symptoms/Findings (n=84)				
Polydipsia	7 (36.84%)	13 (46.43%)	14 (37.84%)	0.732§
Polyuria	8 (42.11%)	11 (39.29%)	10 (27.03%)	0.431§
Abdominal pain	1 (5.26%)	3 (10.71%)	10 (27.03%)	0.082¶
Fatigue	0 (0.00%)	4 (14.29%)	10 (27.03%)*	0.021¶
Dryness of the mouth	0 (0.00%)	1 (3.57%)	2 (5.41%)	0.793¶
Weight loss	3 (15.79%)	6 (21.43%)	3 (8.11%)	0.290¶
Vomiting	5 (26.32%)	6 (21.43%)	18 (48.65%)	0.051§
Headache	0 (0.00%)	0 (0.00%)	2 (5.41%)	0.501¶
Enuresis	1 (5.26%)	2 (7.14%)	1 (2.70%)	0.816¶
Nausea	0 (0.00%)	1 (3.57%)	4 (10.81%)	0.290¶
Hypoglycemia	1 (5.26%)	0 (0.00%)	0 (0.00%)	0.226¶
Lethargy	0 (0.00%)	2 (7.14%)	2 (5.41%)	0.679¶
Back pain	0 (0.00%)	1 (3.57%)	0 (0.00%)	0.560¶
Sweating	0 (0.00%)	1 (3.57%)	0 (0.00%)	0.560¶
Halitosis	1 (5.26%)	0 (0.00%)	0 (0.00%)	0.226¶
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Tachypnea	1 (5.26%)	3 (10.71%)	6 (16.22%)	0.522¶
Polyphagia	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Genital itching	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Fever	0 (0.00%)	0 (0.00%)	3 (8.11%)	0.318¶
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Poor general condition	0 (0.00%)	1 (3.57%)	0 (0.00%)	0.560¶
Growth retardation	0 (0.00%)	0 (0.00%)	0 (0.00%)	-
Hyperglycemia	1 (5.26%)	0 (0.00%)	1 (2.70%)	0.703¶
Dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	-

Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables

According to logistic regression analysis results, vomiting (OR: 16.271; 95% CI: 3.956 - 66.926; p<0.001) and previous DKA history (OR: 21.202; 95% CI: 9.197 - 48.879; p<0.001) were independent risk factors of the diabetic ketoacidosis (Table 7). Other variables included in the analysis, time between symptoms and admission (p=0.081), abdominal pain (p=0.817), fatigue (p=0.279), nausea (p=0.506), lethargy (p=0.222), tachypnea (p=0.131), active infection (p=0.098), diagnosis (p=0.552) were found to be non-significant.

Table 5. Summary of family history and pre- and post-diabetes variables with regard to diabetic ketoacidosis severity

	Diabetic ketoacidosis severity			
	Mild (n=19)	**Moderate (n=28)**	**Severe (n=37)**	**p-value**
Consanguinity (n=73)	2 (11.76%)	6 (26.09%)	7 (21.21%)	0.615¶
Gestational week at birth (n=81)				
Term	18 (94.74%)	26 (100.00%)	33 (91.67%)	0.348¶
Preterm	1 (5.26%)	0 (0.00%)	3 (8.33%)	
Gestational diabetes (n=75)	1 (5.56%)	0 (0.00%)	1 (3.13%)	0.712¶
Diabetes in family/relatives (n=75)	11 (61.11%)	18 (72.00%)	21 (65.63%)	0.746§
Type 1 diabetes in family/relatives	1 (5.56%)	1 (4.00%)	3 (9.38%)	0.845¶
Type 2 diabetes in family/relatives	11 (61.11%)	18 (72.00%)	19 (59.38%)	0.590§
Type of birth (n=80)				
Vaginal birth	12 (63.16%)	15 (60.00%)	20 (55.56%)	0.852§
Cesarean	7 (36.84%)	10 (40.00%)	16 (44.44%)	
Weight at birth, g (n=72)	3320.62±607.43	3492.50±523.28	3320.00±497.27	0.436†
Comorbidity (n=80)	0 (0.00%)	3 (12.00%)	5 (13.89%)	0.273¶
Duration of ketoacidosis, hours (n=71)	6 (4 - 8)	10 (6 - 13)	18.5 (13 - 23)*#	**<0.001**‡
Previous diabetic ketoacidosis history (n=84)	16 (84.21%)	21 (75.00%)	31 (83.78%)	0.617§
Active infection (n=84)	3 (15.79%)	5 (17.86%)	6 (16.22%)	1.000¶
Diagnosis (n=84)				
Type 1 DM	19 (100.00%)	28 (100.00%)	37 (100.00%)	-
Type 2 DM	0 (0.00%)	0 (0.00%)	0 (0.00%)	
MODY	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Tanner stage (n=44)				
Stage 1	9 (75.00%)	8 (66.67%)	13 (65.00%)	0.194¶
Stage 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Stage 3	0 (0.00%)	3 (25.00%)	1 (5.00%)	
Stage 4	0 (0.00%)	1 (8.33%)	2 (10.00%)	
Stage 5	3 (25.00%)	0 (0.00%)	4 (20.00%)	
Length of stay in hospital, days (n=73)	9.5 (3 - 12)	9 (5 - 13)	7.5 (4 - 11)	0.767‡
Stay in intensive care unit (n=73)	1 (6.25%)	0 (0.00%)	10 (30.30%)#	0.002¶
Diagnosis time (n=70)				
Newly diagnosed	8 (50.00%)	14 (60.87%)	15 (48.39%)	0.640§
Previously diagnosed	8 (50.00%)	9 (39.13%)	16 (51.61%)	

MODY: Maturity onset diabetes of the young, DM: Diabetes mellitus, Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile - 75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables, † One-way analysis of variance (ANOVA), ‡ Kruskal Wallis test, § chi-square test, ¶ Fisher-Freeman-Halton test, *Significantly different from "Mild" group, #Significantly different from "Moderate" group. Statistically significant p values are shown in bold

According to logistic regression analysis results, fatigue (OR: 3.981; 95% CI: 1.135 - 13.973; p=0.031) was independent risk factor of the severe DKA (Table 8). Other variables included in the analysis, height (p=0.364) and weight (p=0.078) were found to be non-significant.

Table 6. Summary of laboratory variables with regard to diabetic ketoacidosis severity

	Diabetic ketoacidosis severity			
	Mild (n=19)	**Moderate (n=28)**	**Severe (n=37)**	**p-value**
Blood glucose, mg/dL (n=79)	452.18±150.79	482.92±157.55	488.68±147.38	0.705†
Insulin, µU/mL (n=39)	2 (1.6 - 2.35)	2 (1.43 - 5.65)	6.2 (1.6 - 16)	0.213‡
C-peptide, ng/mL (n=50)	0.17 (0.10 - 0.32)	0.27 (0.17 - 0.40)	0.19 (0.10 - 0.34)	0.234‡
HbA1c, % (n=66)	10.87±2.67	12.25±2.07	12.45±2.11	0.081†
Sodium, mEq/L (n=81)	132.06±4.57	131.78±3.96	135.11±6.79	0.051†
Potassium, mEq/L (n=79)	4.40±0.58	4.00±0.90	4.27±0.76	0.201†
Urea, mg/dL (n=80)	24 (18 - 30)	22 (16 - 30)	27 (20 - 33)	0.389‡
Creatinine, mg/dL (n=80)	0.52 (0.47 - 0.80)	0.63 (0.40 - 0.87)	0.72 (0.51 - 0.86)	0.432‡
Islet autoantibody (n=51)				
Negative	3 (25.00%)	3 (20.00%)	3 (12.50%)	0.641¶
Positive	9 (75.00%)	12 (80.00%)	21 (87.50%)	
WBC ($x10^3$) (n=70)	11.4 (9.9 - 14.8)	11.25 (8.6 - 16.8)	20.1 (13.5 - 34.6)*#	0.001‡
CRP, mg/L (n=70)	0.29 (0.04 - 0.96)	0.22 (0.06 - 0.82)	0.44 (0.19 - 1.05)	0.378‡
Insulin autoantibodies, IU/mL (n=46)	3.8 (0.7 - 7.5)	0.4 (0.4 - 4.3)	2.79 (0.4 - 4.94)	0.292‡
Anti-GAD, IU/mL (n=52)	6.53 (5 - 18.3)	35.08 (5 - 119)	54 (18 - 144)	**0.100‡**
Transglutaminase IgA (n=29)				
Negative	8 (88.89%)	8 (88.89%)	9 (81.82%)	1.000¶
Positive	1 (11.11%)	1 (11.11%)	2 (18.18%)	
Anti-gliadin IgA (n=21)				
Negative	6 (100.00%)	4 (100.00%)	10 (90.91%)	1.000¶
Positive	0 (0.00%)	0 (0.00%)	1 (9.09%)	
Anti-Tg (n=20)				
Negative	3 (100.00%)	4 (66.67%)	9 (81.82%)	0.591¶
Positive	0 (0.00%)	2 (33.33%)	2 (18.18%)	
Anti-TPO (n=20)				
Negative	3 (100.00%)	4 (66.67%)	8 (72.73%)	0.808¶
Positive	0 (0.00%)	2 (33.33%)	3 (27.27%)	
Endomysium IgA (n=28)				
Negative	9 (100.00%)	9 (100.00%)	9 (90.00%)	1.000¶
Positive	0 (0.00%)	0 (0.00%)	1 (10.00%)	

Anti-GAD: Anti-glutamic acid decarboxylase, Anti-TPO: Anti-thyroid peroxidase, CRP: C-reactive protein, HbA1c: Hemoglobin A1c, WBC: White blood cell count, Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile - 75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. † One-way analysis of variance (ANOVA), ‡ Kruskal Wallis test, § chi-square test, ¶ Fisher-Freeman-Halton test, *Significantly different from "Mild" group, #Significantly different from "Moderate" group. Statistically significant p values are shown in bold

Table 7. Significant risk factors independently associated with the development of diabetic ketoacidosis, multivariable logistic regression analysis

	β coefficient	Standard error	p	OR	95% CI for OR	
Vomiting	2.789	0.722	**<0.001**	16.271	3.956	66.926
Previous diabetic ketoacidosis history	3.054	0.426	**<0.001**	21.202	9.197	48.879
Constant	-1.999	0.322	<0.001	0.135		

Nagelkerke R^2=0.574, CI: Confidence interval, OR: Odds ratio

Table 8. Significant risk factors independently associated with the severe diabetic ketoacidosis, multivariable logistic regression analysis

	β coefficient	Standard error	p	OR	95% CI for OR	
Fatigue	1.382	0.641	0.031	3.981	1.135	13.973
Constant	-0.465	0.246	0.058	0.628		

Nagelkerke R^2=0.080, CI: Confidence interval, OR: Odds ratio

Discussion

DKA is a severe metabolic disorder caused by DM-related insulin deficiency and increased counter-regulatory hormones (4). Delayed diagnosis increases the risk of mortality and morbidity, with prognosis being more severe in children. Despite the excessive risks associated with this condition, there are surprisingly few studies that provide comprehensive data encompassing various characteristics of pediatric patients with and without DKA (and in terms of severity). Such data are crucial for the broad comprehension of patient properties and might provide critical information to clinicians and researchers examining this topic, as well as potentially improving the chances for early diagnosis or intervention and reducing preventable complications.

In the current study, DKA was observed at presentation in 84 out of 180 pediatric diabetes cases (46.7%). Despite not being an epidemiological study, our results align with reported DKA rates in pediatric diabetes patients in Türkiye (24.3%-77%) (12-15). An international study based on analyses of three type 1 DM registries [the Prospective Diabetes Follow-up Registry (DPV), the National Paediatric Diabetes Audit (NPDA), and type 1 DM Exchange (T1DX)] reported 1-year DKA incidences of 5% (DPV), 6.4% (NPDA), and 7.1% (T1DX) (16). These studies were based on registries; thus, it would be expected that patients with known diagnosis would present with fewer DKA episodes. The high DKA rate in our study may be attributed to the referral of patients in DKA from other centers and the fact that 58.8% of patients were newly diagnosed with DM at their admission (data available for 136 cases admitted for DM). This is a unique aspect to consider in similar settings, as many pediatric DM diagnoses appear to be made after the patient suffers their first DKA episode – inferring even more importance to the accuracy of diagnosis and its urgency as DKA has a risk for severe morbidities and even mortality. While the general DKA mortality rate in children is estimated at 1%-2%, Sağlam et al. (12) reported a mortality rate of 0.05% in Türkiye. In our study, no mortality was observed.

Clinical symptoms associated with DKA are notable. In our study, symptoms such as abdominal pain, fatigue, vomiting, nausea, lethargy, and tachypnea were significantly more frequent in patients with DKA, consistent with previous findings (17-19). Vomiting was an independent risk factor of the DKA. Classical findings/symptoms of DKA include hyperglycemia (polyuria, polydipsia, nocturia), acidosis (hyperventilation, abdominal pain), and dehydration (dry mucous membranes, lack of tears, poor skin turgor, acute weight loss, and poor perfusion). Abdominal pain can mimic gastroenteritis or acute surgical abdomen (17). These symptoms are primarily driven by increased hepatic ketogenesis due to insulin deficiency and osmotic diuresis caused by hyperglycemia. Vomiting and abdominal pain result from electrolyte loss and metabolic acidosis, often mimicking acute abdomen syndromes. Recognizing these symptoms is critical for early diagnosis and proper management of DKA. The lack of significant differences between DKA severity groups is also notable; however, considering the marginally non-significant differences for some variables (18,19). Our findings align with prior studies emphasizing the role of metabolic acidosis and electrolyte imbalances in triggering

vomiting and abdominal discomfort. However, the absence of significant differences between DKA severity groups in our study suggests that symptom presentation alone may not reliably predict disease severity. Given the marginally non-significant differences observed for some variables, further large-scale studies are needed to clarify potential symptom-based distinctions among severity subgroups.

Other factors associated with DKA are critical for understanding its clinical course. In our study, a history of previous DKA episodes, active infection, and a diagnosis of type 1 diabetes were more common in the DKA group. Notably, a prior history of DKA emerged as an independent risk factor, highlighting the need for targeted interventions in high-risk individuals. This finding aligns with previous studies indicating that patients with recurrent DKA episodes often have suboptimal glycemic control, psychosocial barriers, or inadequate access to healthcare (20). Active infections were present in 16.67% of DKA patients compared to 4.17% in non-DKA patients, a significant difference. In line with this finding, Atkilt et al. (21) reported that 27.8% of patients had infections preceding DKA, while Flood and Chiang (20) found an infection rate of 30.7% in DKA cases. Similar findings were reported in other studies (22,23). Active infections contribute to DKA by increasing insulin resistance and triggering metabolic stress through elevated cortisol and catecholamine levels (24). Therefore, infection detection in patients with DKA is a crucial aspect for management decisions. Notably, none of the type 2 diabetes patients in our study developed DKA, consistent with the established understanding that DKA is primarily a complication of type 1 diabetes. In type 1 diabetes, the lack of insulin leads to fat metabolism for energy production, resulting in the accumulation of ketone bodies and subsequent ketoacidosis (25,26). The higher frequency of intensive care admission in the DKA group reflects the severity of the condition. Intensive care for patients with DKA is typically required due to challenges in correcting severe cases of acidosis, electrolyte imbalance, and dehydration. Previous studies have consistently linked DKA with poor prognosis (27,28).

Summarizing the data presented so far, vomiting and a history of previous DKA episodes emerged as independent risk factors for DKA, highlighting the importance of early recognition and targeted intervention. Careful evaluation of clinical symptoms, particularly gastrointestinal manifestations, along with effective utilization of laboratory findings, remains essential for timely diagnosis and management. Additionally, identifying coexisting factors such as infections can aid in optimizing treatment strategies. Future large-scale studies may provide deeper insights into the mechanisms underlying these risk factors, further improving clinical outcomes in pediatric diabetes patients.

Although DKA is a serious condition by any measure, its severity is still an important parameter that determines the degree of metabolic decompensation and can directly influence treatment strategies (7). Classification allows for better assessment and prioritization of treatment needs. In our study, no significant differences were observed in age and sex among the mild, moderate, and severe DKA groups; however, significant changes in physical and metabolic parameters were identified. Despite similar BMI values, the significant differences in height and body weight in more severe DKA (compared to mild DKA) suggest an impact of body composition on DKA severity. It must also be noted that these variations may be associated with variations in growth characteristics of patients, which might also be influenced by the duration of disease – again indicating the importance of early diagnosis of DM in the pediatric age. The more frequent reporting of fatigue symptoms at presentation in the severe DKA group compared to the mild group is another notable finding despite being based on a relatively small sample size.

In children, the clinical manifestations of DKA often do not align with the severity of acidosis and dehydration. Therefore, children presenting with suspected DKA to outpatient clinics or emergency departments should be considered critically ill until the evaluation is complete (17). In our study, fatigue emerged as an independent risk factor for severe DKA, underscoring its potential role as an early clinical marker of disease severity. The significantly higher leukocyte counts in the severe DKA group compared to both the mild and moderate groups emphasize the importance of the inflammatory response in severe DKA. Additionally, the longer duration of ketoacidosis in the severe group suggests a more treatment-resistant course, reinforcing the need for timely and aggressive management. Moreover, the increased ICU requirements in the severe DKA group compared to the moderate group suggest the need for more aggressive management strategies. Previous studies have associated DKA severity with factors such as age, sex, socioeconomic status, parental education levels, newly diagnosed DM, infections prior to diagnosis, poor glycemic control, and elevated oxidative stress markers (e.g., increased WBC counts, platelet counts, and mean platelet volume) (4,5,7,8). Moreover, longer DKA episodes have been correlated with greater severity, with more severe cases exhibiting altered consciousness, lethargy, Kussmaul breathing, dyspnea, vomiting, tachycardia, and severe dehydration. Laboratory

findings such as hypernatremia are more common in severe DKA cases (marginally non-significant in the present study, p=0.051) and ICU needs are significantly more common in this group (8,29). Our findings contribute to this growing body of evidence by highlighting fatigue as a potential clinical predictor of DKA severity. Moreover, prolonged DKA episodes have been correlated with more severe clinical manifestations, including altered consciousness. Future studies with larger samples may provide a more detailed understanding of the pathophysiological mechanisms underlying the different clinical features associated with DKA severity and contribute to innovative treatment approaches.

Our findings highlight actionable strategies to improve outcomes in pediatric DKA: (1) Early recognition of vomiting, fatigue, and infection can prompt timely diagnosis, especially in new-onset diabetes; (2) High-risk patients (prior DKA, active infections) benefit from intensified monitoring and education; (3) Bedside biomarkers (leukocytosis, acidosis) may guide ICU triage. For public health, increasing awareness of early diabetes symptoms (e.g., polyuria, weight loss) could reduce DKA at presentation. These data support targeted interventions for at-risk children to prevent severe metabolic decompensation.

Study Limitations

As our study was retrospective and single-center in design, the generalizability of our findings may be limited. The retrospective data collection increased the likelihood of missing or inaccurately recorded information and restricted our ability to evaluate all potential risk factors. Due to inconsistently documented timestamps across patient records, we were unable to explore predictors of ICU stay duration and ketoacidosis resolution time. Next, referral bias and the predominance of newly diagnosed diabetes cases may have influenced the findings, potentially limiting the generalizability of the results. Furthermore, the inclusion of a sample from a single center may lead to insufficient representation of populations with diverse socioeconomic statuses and geographical regions. Lastly, the inability to assess the long-term effects of certain risk factors is linked to the cross-sectional nature of this study rather than a longitudinal analysis. Future multicenter, prospective studies with larger sample sizes may overcome these limitations and contribute to a more comprehensive understanding of DKA.

Conclusion

This study presented a comprehensive dataset of pediatric DKA patients at presentation. The frequency of DKA among pediatric patients admitted with DM-related findings was 53.3%. Logistic regression analysis identified vomiting and previous DKA history as independent risk factors for DKA, while fatigue was an independent risk factor for severe DKA. Patients with DKA had a higher frequency of prior DKA episodes, current infection, and ICU admission. More severe metabolic disturbances and increased ICU needs were observed in the severe DKA group. These findings suggest that early identification of vomiting, fatigue, and prior DKA episodes could help clinicians predict the severity of DKA and optimize early intervention strategies. Clinicians should be particularly vigilant in managing patients with a history of DKA and those presenting with concurrent infections, as they are at a higher risk for severe metabolic disturbances. Future studies with larger samples may further elucidate the mechanisms underlying DKA presence and severity, contributing to improved clinical management and the development of targeted preventive measures.

Ethics

Ethics Committee Approval: The study received ethical approval from the Bakırköy Dr. Sadi Konuk Training and Research Ethics Committee (date: 15.05.2017, approval number: 2017-03-20).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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