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Original Article PEDIATRICS

Does the severity of diabetic ketoacidosis in children with type 1 diabetes change during the COVID-19 pandemic? A single-center experience from a pediatric intensive care unit

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ABSTRACT

OBJECTIVE: During the COVID-19 pandemic, health-care services for diseases other than COVID-19 were interrupted, and patient referrals to health institutions were postponed due to their fear of being infected with COVID-19. Under this situation, we conducted this study to evaluate the clinical and laboratory findings of COVID-19 in patients with Type 1 Diabetes Mellitus (T1DM) hospitalized in our pediatric intensive care unit (PICU) with the diagnosis of diabetic ketoacidosis (DKA) during the pandemic period, and the impact of the pandemic on these findings.

METHODS: We retrospectively evaluated 55 children aged from 1 month to 18 years old, diagnosed with DKA, and followed up at Istanbul Sehit Prof. Dr. Ilhan Varank Sancaktepe Training and Research Hospital PICU between April 2020 and December 2021.

RESULTS: A total of 55 patients with DKA as a complication of T1DM were admitted to the PICU during the COVID-19 pandemic. While there was no significant difference in pH and HCO_3 values between those with newly diagnosed T1DM and those with previously-diagnosed T1DM, the HbA1c ratio of newly diagnosed DMs was significantly higher. Of the 55 patients, 4 were COVID-19 PCR positive, and two patients had COVID-19 antibody positivity. When COVID-19 positive patients were compared with negative patients, no significant difference was found between the hospital stay, glucose, HbA1c, lactate, pH, and HCO_3 values.

CONCLUSION: Higher HbA1c levels of newly diagnosed patients presenting with DKA may be associated with delayed admission to the health institutions due to COVID-19 and the length of insulin-free periods compared to pre-diagnosed patients with T1DM. In conclusion, our results, emphasize the importance of physician's and family's awareness of the symptoms of diabetes in terms of early diagnosis and prevention of DKA during public health measures due to COVID-19.

Keywords: COVID-19; diabetic ketoacidosis; pandemic; pediatric intensive care; type 1 DM.

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The World Health Organization declared COVID-19 a pandemic after more than 118,000 cases were detected in the world on March 11, 2020 [1]. SARS-CoV-2 is the type of coronavirus that primarily causes COVID-19, which goes with severe acute respiratory failure [2]. The spread of the virus can occur by

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direct contact with infected people or with contaminated objects. Especially asymptomatic patients play an important role in the spread of the virus [3, 4].

The clinical course of COVID-19 is highly variable, ranging from asymptomatic condition or mild illness to multi-organ failure and even death [5, 6]. Mortality rate varies between 0.7% and 10.8% [7]. Survival decreases and more complications develop in those with advanced age and comorbid diseases [8].

Considering diabetes as a comorbid disease, higher rates of complications and death have been reported in diabetic adults [9]. This situation has raised concerns about the course of COVID-19 in patients diagnosed with Type 1 Diabetes Mellitus (T1DM). In the available literature, data on the course of infection with COVID-19 among children and adolescents with T1DM are controversial [10–13]. In some countries, it has been shown that the indirect effect of COVID-19 prevents patients with T1DM from receiving adequate health services. Thus, interruption of health services for T1DM patients may cause poor glycemic control and more complications [11, 14, 15]. The decrease in applications to the emergency department due to the fear of being infected with COVID-19 has also led to an increase in cases such as diabetic ketoacidosis (DKA), which is one of the T1DM emergencies [11, 16–18]. Therefore, we conducted this review to summarize the prevalence, clinical manifestations, and outcomes of patients with DKA followed in our pediatric intensive care unit (PICU) during the pandemic period.

MATERIALS AND METHODS

Patient Characteristics

We retrospectively evaluated children aged from 1 month to 18 years old, diagnosed with DKA, and followed up at Sehit Prof. Dr. Ilhan Varank Sancaktepe Training and Research Hospital PICU between April 2020 and December 2021. The diagnosis of DKA was made according to the criteria of the American Diabetes Association [19]. Children with nonketotic hyperglycemia and additional comorbidities were excluded from the study. The demographics, clinical, laboratory data, treatment modalities, and length of hospital stay of children with newly or previously-diagnosed T1DM were evaluated.

T1DM was diagnosed by our pediatric endocrinologist if the patients were positive for at least one anti-pancreatic antibody without features suggestive of type 2 diabetes or other forms of diabetes. DKA was defined as the presence of hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dL]), ketonemia, or ketonuria with a pH value of <7.3 and/or a bicarbonate level of <15 mmol/L. Severe DKA was defined as pH <7.1 and/or serum bicarbonate <5 mmol/L [20]. The primary outcome was the evaluation of the frequency, clinical severity, and laboratory findings of DKA patients with new and pre-diagnosed T1DM admitted during the COVID-19 pandemic. Secondary outcomes include the frequency, clinical and biochemical characteristics of patients with DKA with confirmed

Highlight key points

- Of the 55 followed-up patients, 4 were COVID-19 PCR positive and two patients had COVID-19 antibody positivity.
- When COVID-19 positive patients and negative patients were compared, there was no significant difference between the two groups in glucose, HbA1c, lactate, pH, and HCO_3 values.
- While there were 40 patients with pH<7.1, defined as severe DKA, there were 15 patients with pH>7.1.
- Five patients with severe DKAs and 1 patient with DKAs needed mechanical ventilation.

Table 1. Demographic characteristics and laboratory findings of the patients with DKA diagnosed with T1DM

Demographics (n=55)	
Age (years), mean±SD	9.7±4.8
Sex (%)	
Male	36.4
Female	63.6
Diagnose (%)	
Newly diagnosed	70.9
Pre-diagnosed	29.1
Hospital stay, median (min–max)	1.0–34.0
Laboratory findings (n=55)	
Glucose (mg/dl), mean±SD	419.3±139.01
HgbA1c (%), median (min–max)	6.6–16.4
pH, median (min–max)	6.09–7.30
HCO_3, median (min–max)	1.0–20.0
Lactate (mmol/l), median (min–max)	0.5–13.9
Urinary cethone, median (min–max)	+++ (0–+++)
Procalcitonin (µg/l), median (min–max)	0.59 (0.03–177.0)
CRP (mg/l), median (min-max)	2.75 (0.01–118.0)

DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; HCO_3: Actual bicarbonate value in blood gas analysis; CRP: C-reactive protein value; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 2. Characteristic and laboratory data of moderate DKA with severe DKA

Features	pH value		p
	pH <7.1 (n=40)	pH ≥7.1 (n=15)	
Hospitalization day, median (min–max)	3.0 (1.0–34.0)	2.0 (1.0–31.0)	0.455
Mechanical ventilation (n,%)			
Yes (n=6)	5 (83.3)	1 (16.7)	
No (n=49)	35 (71.4)	14 (28.6)	1.00
Laboratory findings, median (min–max)			
Glucose (mg/dl)	414.0 (232.0–946.0)	315.0 (233.0–637.0)	0.098
HbA1c (%)	11.8 (6.6–15.4)	13.1 (9.10–16.4)	0.084
Lactate (mmol/l)	1.85 (0.50–13.90)	1.64 (0.76–2.60)	0.940
HCO_3 (mmol/l)	5.4 (1.0–9.0)	9.38 (5.60–20.0)	**<0.001**
Procalcitonin (µg/l)	0.59 (0.03–177.0)	0.12 (0.04–15.5)	0.508
CRP (mg/dl)	2.69 (0.01–118.0)	2.75 (0.58–25.0)	0.755
AST (U/l)	16.0 (7.0–79.0)	13.5 (9.70–121.0)	0.712
ALT (U/l)	11.5 (5.0–62.0)	11.0 (5.0–71.0)	0.630
LDH (U/l)	240.0 (174.0–572.0)	203.0 (123.0–861.0)	0.074
Albumin (g/l)	42.1 (5.1–197.0)	44.6 (3.6–51.8)	0.438
WBC (10^3 U/l)	20.78 (3.67–51.49)	12.18 (7.30–38.60)	**0.001**
Neutrophil (10^3 U/l)	17.67 (2.5–45.0)	8.6 (5.27–34.1)	**0.001**
Lymphocyte (10^3 U/l)	2.63 (1.18–63.0)	2.69 (1.20–5.23)	0.508
Platelet (10^3 U/l)	319.0 (173.0–540.0)	285.0 (180.0–377.0)	**0.031**
Hemoglobin (g/dl)	13.6 (9.8–16.6)	13.9 (10.8–17.1)	0.202
Na (mmol/l)	138.0 (122.0–151.0)	136.0 (130.0–140.0)	0.066
K (mmol/l)	4.02 (2.08–114.0)	3.57 (3.10–5.40)	0.273
Na (24 h)	139.5 (132.0–156.0)	138.0 (135.0–150.0)	0.148
K (24 h)	3.59 (2.6–5.1)	3.4 (2.5–4.4)	0.363
Glucose (24 h)	202.5 (97.0–448.0)	172.0 (94.0–288.0)	0.076
HCO_3 (24 h)	16.6 (12.0–28.1)	21.0 (16.0–30.0)	**<0.001**

DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; HCO_3: Actual bicarbonate value in blood gas analysis; CRP: C-reactıve protein value; AST: Aspartate amino transferase; ALT: Alanine amino transferase; LDH: Lactate dehydrogenase; WBC: White blood cell count; Na: Serum sodium value; K: Serum potassium value.

COVID-19 diagnosis based on COVID-19 PCR positive test and/or COVID-19 antibody-positive test.

Informed consent was obtained from all parents before hospitalization and during all procedures. Non-invasive Clinical Research Ethics Committee approval was received from Hospital at Sehit Prof. Dr. Ilhan Varank Sancaktepe institution (12.04.22 E-46059653-020-552). This study was carried out in accordance with the Declaration of Helsinki Principles.

Statistical Analysis

Age at the time of diagnosis, length of hospital stay, duration of subcutaneous insulin use, laboratory data and blood gas values, minimum, maximum, and median values of all T1DM patients hospitalized with the diagnosis of DKA in the PICU opened during the COVID-19 pandemic were used. Hospitalization times, laboratory data, and blood gas values of DKA patients with positive PCR and/or ab were compared. IBM SPSS Statistics-20 (Statistical Package for the Social Sciences version 20, IBM Corp., Armonk, NY) program was used for the analyzes to be carried out within the scope of the research. Using SPSS software, parametric tests were applied for parameters with normal distribution according to their distribution characteristics, and non-parametric tests were applied for parameters with the abnormal distribution.

Table 3. Characteristics and laboratory data of patients presenting with DKA as a complication of diagnosed T1DM with newly diagnosed T1DM

Features	Diagnosis time		p
	New diagnose (n=39)	Known diagnose (n=16)	
Hospital stay, median (min–max)	3.0 (1.0–34.0)	3.0 (1.0–31.0)	0.775
Mechanical ventilation (n,%)			
Yes (n=6)	4 (66.7)	2 (33.3)	
No (n=49)	35 (71.4)	14 (28.6)	1.00
Laboratory findings, median (min–max)			
Glucose (mg/dl)	411.0 (233.0–946.0)	394.5 (232.0–759.0)	0.566
HbA1c (%)	12.9 (9.0–16.4)	10.7 (6.6–14.7)	0.002
pH	7.02 (6.09–7.27)	7.02 (6.82–7.30)	0.882
Lactate (mmol/l)	1.6 (0.5–13.9)	2.3 (0.6–7.7)	0.115
HCO_3 (mmol/l)	5.9 (1.0–19.0)	6.4 (3.7–20.0)	0.956
Procalcitonin (µg/l)	0.54 (0.03–177.0)	3.21 (0.05–15.5)	0.064
CRP (mg/dl)	2.63 (0.01–30.2)	3.38 (0.01–118.0)	0.649
AST (U/l)	14.0 (7.3–41.0)	21.7 (7.0–121.0)	0.035
ALT (U/l)	10.7 (5.0–37.1)	16.4 (5.0–71.0)	0.009
LDH (U/l)	222.0 (123.0–383.0)	240.0 (154.0–861.0)	0.266
Albumin (g/l)	41.9 (3.6–51.8)	43.5 (5.1–197.0)	0.278
WBC (10^3 U/l)	16.15 (3.67–37.0)	23.35 (9.10–51.49)	0.021
Neutrophil (10^3 U/l)	12.15 (2.5–29.4)	18.65 (5.27–45.0)	0.020
Lymphocyte (10^3 U/l)	2.63 (1.18–63.0)	2.87 (1.27–6.80)	0.704
Platelet (10^3 U/l)	299.0 (173.0–540.0)	340.5 (180.0–501.0)	0.326
Hemoglobin (g/dl)	13.3 (9.8–17.1)	14.2 (11.2–16.6)	0.221
Na (mmol/l)	137.0 (122.0–151.0)	137.0 (128.0–145.0)	1.00
K (mmol/l)	3.7 (2.9–114.0)	4.8 (3.1–6.0)	0.003
Na (24 h)	139.0 (133.0–156.0)	139.0 (132.0–149.0)	0.985
K (24 h)	3.3 (2.5–5.05)	3.9 (3.1–4.6)	0.005
Glucose (24 h)	188.0 (94.0–320.0)	185.0 (133.0–448.0)	0.970
pH (24 h)	7.36 (7.0–7.45)	7.35 (7.20–7.43)	0.717
HCO_3 (24 h)	17.3 (12.0–30.0)	18.2 (12.1–28.6)	0.475

DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; HCO_3: Actual bicarbonate value in blood gas analysis; CRP: C-reactıve protein value; AST: Aspartate amino transferase; ALT: Alanine amino transferase; LDH: Lactate dehydrogenase; WBC: White blood cell count; Na: Serum sodium value; K: Serum potassium value.

Appropriate correlation analyzes were performed between the parameters. To evaluate the statistical significance of the findings obtained as a result of these analyzes, the findings were interpreted by considering the $p<0.05$ threshold value.

RESULTS

Between April 2020 and December 2021, which is the COVID-19 pandemic period, 55 patients with DKA as a complication of T1DM were followed up in our PICU. The mean age of the patients was 9.7±4.8 years and 70.9% of them were newly diagnosed, while 29.1% were pre-diagnosed with T1DM. Of 55 patients, 35 (63.6%) were female, and 20 (36.4%) were male. The median hospital stay was 3.0 (1.0–34.0) days and the median values of pH, HCO_3 and HbA1c were 7.02 (6.09–7.30), 5.9 (1.0–20.0), and 12.1% (6.6–16.4), respectively. None of our patients died during the course of the DKA attack (Table 1).

While there were 40 patients with pH <7.1, defined as severe DKA, there were 15 patients with pH>7.1. Five patients with severe DKAs and 1 patient with DKAs

Table 4. Clinical characteristics and laboratory data of patients with COVID-19 positive T1DM presenting with DKA

	COVID-19 PCR + (n=4)				COVID-19 Anti-body + (n=2)	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (months)	38.0	174.0	107.0	62.0	136.0	167.0
Sex	Female	Female	Male	Female	Male	Male
Diagnose	New diagnose	New diagnose	New diagnose	New diagnose	New diagnose	New diagnose
Subcutaneous insulin time	24.0	20.0	24.0	22.0	336.0	96.0
Glucose (mg/dl)	496.0	390.0	657.0	356.0	946.0	321.0
HgbA1c (%)	10.70	13.00	11.20	12.90	13.30	15.00
pH	6.99	6.90	6.89	7.09	6.90	7.01
HCO_3 (mmol/l)	6.90	5.90	5.80	4.80	5.20	5.40
Lactate (mmol/l)	2.0	0.5	1.90	0.95	1.70	1.0
Urinary ke-tone	+	+	+++	+++	+++	+
Procalcitonin (µg/l)	1.64	0.59	–	0.29	0.23	0.03
CRP (mg/l)	1.02	24.2	0.40	14.15	0.60	0.60

DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; HCO_3: Actual bicarbonate value in blood gas analysis; CRP: C-reactıve proteın value.

needed mechanical ventilation. The median HbA1c value of patients with severe DKA was 11.8 (6.6–15.4), and in patients with moderate DKA was 13.1 (9.10–16.4), there was not a statistically significant difference in the duration of hospitalization, duration of mechanical ventilation and laboratory parameters between two groups (Table 2).

Of the patients followed with DKA, 39 were newly diagnosed and 16 were pre-diagnosed with T1DM. Four of the newly diagnosed DKA patients and 2 of the previously-diagnosed T1DM patients needed mechanical ventilation. Although there is no significant difference in pH and HCO_3 values between those with newly diagnosed T1DM and previously-diagnosed T1DM, the median HbA1c value of newly diagnosed T1DM was 12.9 (9.0–16.4), and in previously-diagnosed T1DM was 10.7 (6.6–14.7) and the difference was statistically significant ($p<0.005$) (Table 3).

Of the 55 followed-up patients, 4 were COVID-19 PCR positive and 2 patients had COVID-19 antibody positivity. All of the COVID-19- positive patients were newly diagnosed with T1DM and their laboratory data are given in Table 4.

When COVID-19 positive patients and negative patients were compared, the median number of hospital stay was found to be 3 days in both groups. There was no significant difference between the two groups in glucose, HbA1c, lactate, pH, and HCO_3 values (Table 5).

DISCUSSION

In the study conducted in Brazil for PICU hospitalizations in DKA patients, it was observed that 52 patients were followed in 2 years [21], and 32 patients were followed in a 5-year study in Pakistan [22]. Although our study was conducted in the PICU, which was opened during the pandemic period, within 18 months, 55 patients with DKA as a complication of T1DM were followed up. The number of DKA patients as a complication of T1DM followed in our PICU within 18 months is higher compared to the literature.

In a multicenter study conducted in Saudi Arabia during the COVID-19 pandemic period, no significant difference was found between the HbA1c values of newly diagnosed DMs and diagnosed T1DMs without DKA [17]. On the other hand, in a multi-center study from Turkiye, it is reported that the frequency of new onset of Turkiye 1 diabetes and severe cases among children was increased and the cause of the increased severe presentation might be related to restrictions related to the pandemic [23]. Similarly, in some recent studies, it was evaluated that higher HbA1c levels of DKA patients presenting with newly diagnosed T1DM were associated with delayed admission to the hospital due to COVID-19 and the length of insulin-free periods compared to patients with previously-diagnosed. The reason

Table 5. Hospitalization time and laboratory data of patients with T1DM diagnosed with DKA and followed by the presence of COVID

Features	COVID-19 + patients (n=6)	COVID-patients (n=49)	p
Hospitalization day, median (min–max)	3.0 (1.0–34.0)	3.0 (1.0–31.0)	0.967
Laboratory findings, median (min–max)			
Glucose (mg/dl)	443.0 (321.0–946.0)	411.0 (232.0–759.0)	0.230
HbA1c (%)	12.9 (10.7–15.0)	12.1 (6.6–16.4)	0.084
Lactate (mmol/l)	1.4 (0.5–2.0)	1.8 (0.6–13.9)	0.190
HCO_3 (mmol/l)	5.6 (4.8–6.9)	6.2 (1.0–20.0)	0.366
pH	6.95 (6.89–7.09)	7.04 (6.1–7.30)	0.267

DKA: Diabetic ketoacidosis; T1DM: Type 1 diabetes mellitus; HCO_3: Actual bicarbonate value in blood gas analysis.

for delayed admission of patients with T1DM may be similar to those reported in other countries, such as the focus of healthcare professionals on clinical signs related to COVID-19. In addition, parents avoided seeking medical attention while their symptoms were mild, due to the children's fear of being infected with COVID-19 in the hospital and difficulties in accessing healthcare due to quarantine [21–24]. One of the interesting data we obtained in this study was that the severity of the disease was not statistically significant between DKA patients with new and previously-diagnosed T1DM. However, the HbA1c levels of newly diagnosed T1DM were higher than in those with previously-diagnosed T1DM. In our opinion, the prolonged insulin-free period is strongly related to the higher HbA1c levels, especially in children with newly diagnosed T1DM.

There are limited data on the course of COVID-19 infection among children with previously-diagnosed T1DM [22]. COVID-19 confirmed adults with diabetes who showed a severe course of illness and poor outcome, while studies in children with diabetes have shown a milder course and better outcome [16, 25–28]. In our study, similar to the literature, no significant difference was found between the number of days of hospitalization, glucose, HbA1c, lactate, pH, and HCO_3 values between COVID-19 positive and negative DKA patient.

In accordance with the previous studies and the data we obtained, it was shown that the pandemic significantly affected children with T1DM by the conditions during the pandemic that caused a delay in the diagnosis and treatment of diabetes. These data show that in addition to the requirement that the pandemic conditions continue at a standard level for children with pre-diagnosed or undiagnosed T1DM to access healthcare services, continuous awareness of T1DM should be provided, especially among health-care professionals working in the pediatric field.

Limitation

The number of patients is limited as our study is a study conducted in a single-center PICU. Moreover, since our PICU was opened during the pandemic period, a comparison could not be made with the patients who presented with DKA as a complication of T1DM before the pandemic.

Conclusion

Since our PICU was opened during the pandemic period, when we compared the data of our patients who were followed up with the diagnosis of DKA with the data in the literature we did not detect a significant difference in the severity of our patients. Higher HbA1c levels of newly diagnosed patients presenting with DKA may be associated with delayed admission to the health institutions due to COVID-19 and the length of insulin-free periods compared to pre-diagnosed patients with T1DM. Our results, emphasize the importance of physician's and family's awareness of the symptoms of diabetes in terms of early diagnosis and prevention of DKA during public health measures due to COVID-19.

Ethics Committee Approval: The Health Science University, Sehit Prof. Dr. Ilhan Varank Sancaktepe Training and Research Hospital Non-Interventional Research Ethics Committee granted approval for this study (date: 13.04.2022, number: E-46059653-020-324).

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Authorship Contributions: Concept – FV, LGBO; Design – FV; Supervision – FV, HC; Fundings – FV, EGS, YYC; Materials – EGS, YYC; Data collection and/or processing – FV, LGBO; Analysis and/or interpretation – FV, UA; Literature review – FV, UA; Writing – FV; Critical review – HC.

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