

Diabetic Ketoacidosis Before, During, and After The COVID-19 Pandemic

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Abstract

Background: Diabetic ketoacidosis (DKA) can be the initial sign of type 1 diabetes in children upon diagnosis. Some studies have examined the impact of the coronavirus disease 2019 (COVID-19) pandemic on the incidence and severity of DKA in children. The aim of this study was to investigate the status of diabetic ketoacidosis before and during COVID-19.

Methods: This cross-sectional study was conducted at Akbar Pediatric Super-specialty Hospital in Mashhad and included one year before and one year after the start of the COVID-19 pandemic. All children under 18 years old admitted with a diagnosis of DKA based on the 2018 international society for pediatric and adolescent diabetes (ISPAD) protocol were included in the study. A checklist was completed for each patient, and the data was entered into SPSS software for analysis. A significance level of 0.05 was set for all inferential statistical tests.

Results: A total of 310 patients were included in the study, of which 176 (56.8%) were male and the rest were female. In 2018, only 33% of new cases were diabetic, while in 2020, this rate had reached 57.2% ($p=0.006$). 18.4% of patients during the COVID-19 era had bicarbonate levels less than 5 upon admission, whereas during the pre-COVID era, only 5.3% of patients had bicarbonate levels less than 5. The rate of Intensive care unit (ICU) admission in 2020 was significantly higher than in 2018 ($p=0.003$), with 15.9% of patients being admitted to the ICU in 2020.

Conclusion: Based on the results of our study, the rate of patients diagnosed with diabetes and diabetic ketoacidosis significantly increased during and after the COVID-19 pandemic.

Key Words: Children, COVID-19, Diabetes, Diabetic ketoacidosis.

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1- INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic created a serious health crisis with severe morbidity and mortality worldwide. Due to restrictions imposed in countries, visits by patients with chronic diseases and the use of healthcare decreased, and consequently, the receipt of medical services was delayed (1).

The recommendation to stay at home led to a decrease in visits to healthcare centers and a reduction in the receipt of medical services for children, significantly increasing concerns about the diagnosis of other diseases, including diabetes, in children (2).

In most children, diabetes manifests with symptoms such as polydipsia, polyuria, and weight loss, but sometimes diabetic ketoacidosis (DKA) can be the first manifestation of type 1 diabetes in children at the time of diagnosis (3). Diabetic ketoacidosis is a severe and potentially life-threatening manifestation of diabetes that can lead to significant morbidity in children (4).

SARS-CoV-2, by using the angiotensin-converting enzyme 2 (ACE-2) receptor to penetrate cells, may also directly cause diabetic ketoacidosis (5). There is also the possibility that COVID-19 alone can directly cause damage to pancreatic beta cells (6). Furthermore, in children with coronavirus disease 2019 (COVID-19), the diagnosis of type 1 diabetes may be accelerated (7, 8).

There are studies regarding the impact of the COVID-19 pandemic on the incidence and severity of DKA in children. Some of these studies have reported an increase in the incidence of DKA during this pandemic (9, 10), while others have not reported any change in the incidence and severity of diabetic ketoacidosis (11).

The present study was conducted to determine the characteristics, clinical, and laboratory features of children with diabetic ketoacidosis during the COVID-19 pandemic, and to compare them with the period before the pandemic.

2- MATERIALS AND METHODS

This cross-sectional study was conducted at Akbar Pediatric Super-specialty Hospital in Mashhad, including one year before and one year after the start of the COVID-19 pandemic. All children under 18 years old admitted with a diagnosis of DKA based on the 2018 international society for pediatric and adolescent diabetes (ISPAD) protocol (12) were included in the study. A checklist was completed for each patient, including demographic information (such as age, gender, place of residence, etc.), clinical symptoms at the time of admission (abdominal pain, nausea and vomiting, decreased consciousness, neurological symptoms, etc.), the time interval from symptom onset to physician visit, laboratory findings (PH, HCO₃⁻, COVID-19 polymerase chain reaction (PCR) nasopharynx), and Intensive care unit (ICU) admission. Patient information from 2018 was reviewed from patient files available in the hospital archives.

The severity of DKA is defined by the degree of acidosis: mild, (venous pH 7.2 to 7.3 or serum bicarbonate 10 to 15 mmol/L), moderate (pH 7.1 to 7.2 or serum bicarbonate 5 to less than 10 mmol/L), and severe (pH under 7.1 or serum bicarbonate less than 5 mmol/L).

After inputting the data into statistical package for the social sciences (SPSS) version 22, descriptive statistics such as frequency, percentage, mean, and standard deviation were calculated. For the analysis, either the chi-square test, t-test, or appropriate nonparametric alternatives were employed. A significance level of

0.05 was set for all inferential statistical tests.

All stages of the study followed the ethical principles of the Helsinki Declaration and were approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1400.745).

3- RESULTS

A total of 310 patients were enrolled in the study, of whom 176 (56.8%) were male and the remaining were female. Table 1 provides a detailed overview of the demographic profiles of the patients who participated in this study.

Table-1. Demographic characteristics of patients included in the study.

Characteristic		Frequency (percentage) or SD±Standard deviation
Gender	Female	134 (%43.2)
	Male	176(%56.8)
Age (years)		9.16±4.08
Time of admission	2018	39 (%12.6)
	2020	271(%87.4)
Diabetes mellitus status	New case	141 (%45.8)
	Known case	167 (%54.2)
Duration of departure from DKA. (Hours)		19.77±13.82
Underlying disease		18(%5.8%)

The most common clinical symptoms were polyuria and polydipsia, reported in 65.8% and 64.8% of patients, respectively.

A comparison was made of the demographic characteristics of patients

referred in 2018 and 2020 were compared. As shown in Table 2, in 2018, only 33% of new cases had diabetes, while in 2020 this rate had increased to 57.5%.

Table-2. Demographic and clinical characteristics of patients included in the study by year.

Variable		Time of admission Frequency (percentage) or SD±Standard deviation		P value
		2018	2020	
Gender	Female	20 (51.3)	156(57.7)	*0.492
	Male	19(48.7)	115(42.4)	
Age(years)		10.02±3.75	9.04±4.12	**0.166
Diabetes mellitus status	New case	13(33.3)	156(57.5)	*0.006
	Known case	26(66.7)	115(42.4)	
Duration of departure from DKA. (Hours)		20.27±15.75	19.66±13.42	**0.814
Underlying disease		0(0)	18(66.6)	*0.143

* Fisher's exact test.

** Independent T-test.

In Table 3 the clinical symptoms of patients included in the study in 2018 and 2020 are compared. A comparison of

patients' laboratory findings was conducted between 2018 and 2020, and the results are presented in Table 4.

Table-3. Comparison of clinical symptoms of patients by year.

Clinical finding	Time of admission Frequency (percentage)		*P value
	2018	2020	
Polyuria	25(64.1)	179(67.3)	0.717
Polydipsia	26(66.7)	175(65.8)	>0.999
Polyphagia	3(7.7)	60(22.4)	0.034
Weight loss	11(28.2)	127(47.6)	0.025
Tachycardia	0(0)	77(28.7)	<0.001
Tachypnea	0(0)	90(33.6)	<0.001
Abdominal pain	29(74.4)	100(37.5)	<0.001
Vomiting	34(87.2)	109(40.8)	<0.001
Weakness	1(2.6)	182(68.2)	<0.001

* Fisher's exact test.

Table-4. Comparison of patients' laboratory findings between 2018 and 2020.

laboratory findings		Time of admission Frequency (percentage)		P value
		2018	2020	
WBC 10 ⁶ /l	Less than 4000	0 (0)	2(0.8)	*0.024
	4000-11000	13(36.1)	155(59.2)	
	More than 11000	23(63.9)	105(40.1)	
PMN %	Less than 45%	1((2.8)	53(25.2)	*0.005
	45-75%	22(61.1)	113(53.8)	
	More than 75%	13(36.1)	44(21)	
Lymph %	Less than 20%	11(30.6)	59(28.5)	*0.053
	20-45%	23(63.9)	101(48.8)	
	More than 45%	2(5.6)	47(22.7)	
Hb g/dl	Less than 11	7(21.2)	18(6.9)	*0.017
	11-13	7(21.2)	82(31.3)	
	More than 13	19(57.6)	162(61.8)	
PLT 10 ⁶ /l	Less than 150	1(3.29)	9(3.5)	*0.267
	150-450	24(77.4)	222(86.7)	
	More than 450	6(19.4)	25(9.8)	
PH	Less than 7.1	10(26.3)	45(17.6)	*0.008
	7.1-7.2	25(60.5)	111(43.5)	
	More than 7.2	5(13.2)	99(38.8)	
Bicarbonate meq/l	Less than 5	2(5.3)	47(18.4)	*0.206
	5-10.99	12(31.6)	64(24.1)	
	11-14.99	12(31.6)	55(21.6)	
	15	0(0)	3(1.2)	
	More than 15	12(31.6)	86(33.7)	
ESR mm/h	Less than 10	6(21.4)	71(33.3)	**0.281
	≥10	22(78.6)	142(66.7)	
CRP mg/dl	Less than 6	14(56)	173(80.5)	**0.010
	≥6	11(44)	42(19.5)	

Abbreviation. **WBC:** White blood cell; **PMN:** Polymorphonuclear leukocyte; **Lymph:** Lymphocyte; **PLT:** Platelet; **Hb:** Hemoglobin; **ESR:** Erythrocyte sedimentation rate; **CRP :** C-reactive protein.

* Chi-square test. ** Fisher's exact test.

It should be noted that the COVID PCR test was positive in 7 patients (2.3%).

The rate of ICU admission in 2020 was significantly higher than in 2018 ($p=0.003$), with 15.9% of patients being admitted to the ICU in 2020.

The results showing the total number of hospitalizations due to diabetes and diabetic ketoacidosis by year are presented in Figure 1. It is evident that hospitalizations for diabetes and diabetic ketoacidosis have increased significantly following the COVID-19 pandemic.

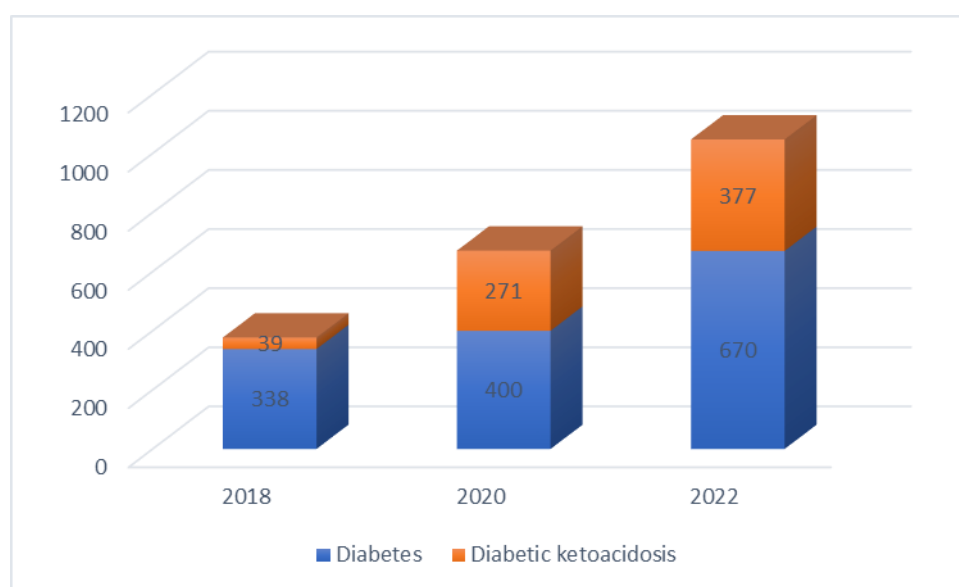


Figure-1: Comparison of the number of hospitalizations due to diabetes and diabetic ketoacidosis by year.

4- DISCUSSION

The results obtained from our study indicated that, overall, 45% of patients with DKA were newly diagnosed cases of diabetes. Comparing 2018 with 2020, it was shown that the rate of newly diagnosed cases in 2020 was significantly higher than in 2018. In 2018, one-third of patients were newly diagnosed, but in 2020, over 57% of all patients were newly diagnosed cases of type 1 diabetes.

The most common clinical symptoms of patients admitted to our study were polyuria, polydipsia, weakness, vomiting, weight loss, and abdominal pain, respectively. Less common symptoms included tachypnea, tachycardia, and polyphagia. A comparison of the clinical symptoms of patients between the two years under review showed that abdominal pain and vomiting were more common in

patients admitted in 2018 than in patients admitted during the COVID-19 pandemic. Conversely, symptoms such as polyphagia, weight loss, and weakness were reported more frequently in patients admitted during the COVID-19 pandemic.

In laboratory examinations, nearly 19% of patients had a pH below 7.1, indicating severe diabetic ketoacidosis. In 26%, the pH was between 7.1 and 7.2 (moderate ketoacidosis), and in another 35%, it was above 7.2. Comparing the years 2018 and 2020, it was shown that the frequency of patients with severe ketoacidosis in 2020 was significantly lower than in 2018. Also, leukocytosis and high C-reactive protein (CRP) were significantly more observed in patients hospitalized in 2018 than in patients hospitalized in 2020. However, it should be noted that the number of patients in 2018 was much lower than in 2020.

In a study conducted in 2021 by Bogale et al. in the United States, the authors investigated the impact of COVID-19 on the incidence of DKA in children with newly diagnosed type 1 diabetes. For this purpose, patients who visited a center in that country between 2017 and 2020 were examined. The results showed that the rate of COVID-19 diagnosis before and after the COVID-19 pandemic was similar, and the severity of DKA did not differ before and after COVID-19 (13% of patients had mild DKA before COVID-19, and 14% after COVID-19). The average age of patients was approximately 10 years both before and after COVID-19, and in both periods, more than half of the patients were male (13).

The results obtained in our study regarding the gender and age of patients are similar to the findings of Bogale et al.'s study, as in both studies, the frequency of DKA was higher in males, and the average age of referred patients was near to 10 years. However, in our study, a larger number of patients were admitted to the ICU during the COVID period, which may indicate a greater severity of diabetic ketoacidosis during that time, which is inconsistent with the findings of Bogale et al. The reason for the different results of the two studies in this regard cannot be precisely determined. It should be noted that the sample size of our study in the group of patients hospitalized before the COVID-19 outbreak was relatively small, and this may have led to a decrease in the accuracy of the obtained results. Also, in our study, both newly diagnosed patients and known patients with type 1 diabetes were included, while Bogale et al. only examined newly diagnosed patients, which could also have led to different results in the two studies.

In a study by Ho et al. in Canada, the authors investigated the incidence and severity of DKA in newly diagnosed

patients with type 1 diabetes. For this purpose, 114 children admitted in 2019 were compared with 107 children admitted in 2020. The results showed a significant increase in DKA incidence in 2020, and severe DKA was reported at 27.1% in 2020 versus 13.2% in 2019 (14).

Similarly, in our study, the frequency of DKA during the COVID-19 era was significantly higher than in the pre-COVID-19 era and in our research, 18.4% of patients during the COVID-19 era had bicarbonate levels less than 5 upon admission, whereas during the pre-COVID era, only 5.3% of patients had bicarbonate levels less than 5.

Loh et al., in a study published in 2021, investigated diabetic ketoacidosis in 125 children with type 1 and 2 diabetes during the COVID-19 pandemic in Germany. For this purpose, clinical and laboratory data of patients under 18 years old, who were newly diagnosed with diabetes or had a known history of diabetes, were compared during the COVID-19 period with the year prior. The results showed that in both time periods, the frequency of female patients was higher than male patients. Also, in terms of age, the average age of patients in both time periods was approximately 10 years. Finally, the average blood pH of patients before COVID-19 was reported as 7.30 and during COVID-19 as 7.27, and the difference in DKA severity between these two time periods was not significant (15).

In our study, unlike the study by Loh et al., DKA was more common in males than in females. In terms of age, patients in both groups were almost similar. Regarding DKA severity, in our study, the DKA severity of patients hospitalized before the COVID-19 period was different, which is inconsistent with the findings of Loh et al.'s study. The exact reason for the different results obtained in the two studies

cannot be determined. However, it should be noted that the sample size of our study was approximately twice the sample size of Loh et al.'s study, which may have increased the accuracy of the results obtained in our study.

In another study in Saudi Arabia published by Alaqeel et al. in 2021, the authors investigated the frequency of new-onset type 1 diabetes and DKA during and before COVID-19 in 6 hospitals in that country. A total of 260 participants were included in the study. The results showed that, overall, during COVID-19, a larger proportion of DKA cases were newly diagnosed (before COVID-19, 13% were newly diagnosed, and after COVID-19, 26%). In terms of demographics, the average age of patients in both time periods was close to 10 years, and approximately 55% of patients in both time periods were female (4).

In our study, similarly to Alaqeel et al.'s research, the age and gender composition of DKA patients in the pre- and post-COVID-19 periods did not show a significant difference. Also, in both studies, similarly, the frequency of newly diagnosed diabetes was higher in patients who presented during the COVID-19 period compared to patients who were hospitalized before COVID-19.

In our study and some other studies conducted in other countries, the incidence of newly diagnosed diabetes in patients hospitalized due to DKA during the COVID-19 era was higher than in the pre-COVID era. The reason for this is likely that during the COVID-19 era, due to the healthcare system's focus on controlling the epidemic and its related clinical symptoms, there may have been a delay in diagnosing children with type 1 diabetes, leading to the occurrence of DKA in patients. On the other hand, given that during the COVID-19 era, governments strongly advised parents not to leave home unless necessary, it is probable that

patients did not seek medical attention at the onset of symptoms, and therefore, patients presented when DKA had already developed.

A study conducted in Isfahan found that the incidence of type 1 diabetes (T1D) rose, especially during the second year of the COVID-19 pandemic. Although several other studies have similarly reported higher T1D case numbers, the multifaceted process behind T1D development means it's difficult to make firm conclusions about the direct influence of SARS-CoV-2 infection on the onset of T1D (16).

Noura M. Ibrahim Elbakry et al proved that the COVID-19 pandemic has resulted in a rise in the number of children reporting newly diagnosed diabetes, and in more people with newly diagnosed diabetes reporting severe DKA (17).

In the last two studies, similar to ours, an increase in the incidence of new diabetes cases during the COVID-19 pandemic has been reported.

A larger study in more ethnically mixed populations could be conducted in a multicenter fashion and yield more meaningful data to assess the behavior of COVID-19 on the incidence and prevalence of Type 1 Diabetes Mellitus (T1DM). In conclusion new T1DM cases were considerably higher during the pandemic era, which implies more incidence of T1DM during the pandemic.

5- CONCLUSION

Based on the results of our study, the rate of patients diagnosed with diabetes and diabetic ketoacidosis significantly increased during and after the COVID-19 pandemic. It appears that further extensive and multi-center research is necessary to confirm the virus's role in the occurrence of diabetic ketoacidosis and diabetes.

6-ABBREVIATION

WBC: White blood cell; **PMN:** Polymorphonuclear leukocyte; **Lymph:** Lymphocyte; **PLT:** Platelet; **Hb:** Hemoglobin; **ESR:** Erythrocyte sedimentation rate; **CRP :** C-reactive protein

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