ORIGINAL ARTICLE

The Effect of the SARS-CoV-2 Pandemic on Presentation with Diabetic Ketoacidosis in Children with New Onset Type 1 Diabetes Mellitus

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What is already known on this topic?

In children with type 1 diabetes mellitus (T1DM), there may be decreased neutrophil function, T-cell response and abnormal humoral immunity, any or all of which may result in increased susceptibility to various infections. These infections may trigger acute complications of T1DM including diabetic ketoacidosis (DKA) and, on some occasions, hypoglycemia.

What this study adds?

Although there was no increase in the frequency of DKA in our study, an increase was observed in severe DKA cases. First-line clinicians should encourage information on early diagnosis, and children with new-onset T1D and/or DKA symptoms should have prompt access to experienced teams.

Abstract

Objective: Diabetic ketoacidosis (DKA) is a life-threatening, acute complication of type 1 diabetes mellitus (T1DM). Infection is the most common precipitating factor for DKA, being responsible for more than 50% of such complications. The frequency and severity of DKA in children with T1DM, before and during the coronavirus disease 2019 outbreak were evaluated and compared with pre-pandemic presentation and severity rates.

Methods: In total, 199 patients younger than 18 years were included in the study. Patients were divided into two groups: the Coronavirus disease-2019 (COVID-19) pandemic group (new onset T1DM presenting from March 2020 to March 2021; the control group included new onset T1DM from March 2016 to March 2020.

Results: The rate of DKA at presentation was similar (p = 0.393) during the pandemic period (58.3%) compared to the pre-pandemic years (44.8-64.3%). Although the percentage of DKA was similar, the rate of severe DKA in the COVID-19 group was higher than previous years. Although not significant, the duration of diabetes symptoms was longer in the COVID-19 period than the previous years.

Conclusion: This study suggests that the rate of severe DKA, but not the overall rate of DKA, has increased during the COVID-19 pandemic compared to the prior four years. This may be due to the behavior of the parents of sick children and the limited access to the healthcare system. Despite this limited access, parental concern may have been sufficiently high to seek medical attention for their children, avoiding an increased frequency of DKA as the first presentation of new-onset T1DM.

Keywords: Type 1 diabetes mellitus, diabetic ketoacidosis, Coronavirus disease-2019

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Introduction

Type 1 diabetes mellitus (T1DM) is characterized by chronic immune-mediated destruction of pancreatic β cells leading to partial or absolute insulin deficiency. In the majority of cases, T1DM results from autoimmune-mediated pancreatic β-cell destruction and is influenced by different factors, such as genes, age, and ethnicity (1). In children with T1DM, there may be decreased neutrophil function, T-cell response and abnormal humoral immunity, which may result in increased susceptibility to various infections (2,3). These infections may trigger acute complications of T1DM, including diabetic ketoacidosis (DKA), a potentially severe and life threatening condition, and in some occasions, hypoglycemia. There are reports about the relationship between fulminant DM and different infections (4,5,6,7), but such reports involving Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection are rare (8). However, infection is often a precipitating factor for DKA and has been reported to be responsible for more than half of cases (9).

Pancreatic β cell function may deteriorate after Coronavirus disease-2019 (COVID-19), and this may trigger DKA in diabetic patients (10). The aim of this study was to determine the clinical characteristics and frequency of DKA in children diagnosed with T1DM during the COVID-19 pandemic and to compare this with similar characterisitics in patients presenting in the pre-COVID-19 years.

Methods

The study population included children less than 18 years of age presenting with new onset T1DM. The COVID-19 pandemic group comprised those presenting with new onset T1DM from March 2020 to March 2021. The control group included new onset T1DM presenting from March 2016 to March 2020.

Patients with syndromic diabetes, type 2 diabetes, maturity onset diabetes in the young, and secondary diabetes due to any cause, such as cystic fibrosis, steroid use or lipodystrophy, were excluded. Patient data were analyzed by retrospective review of medical records. All patients were diagnosed with T1DM according to the guidelines of the International Pediatric and Adolescent Diabetes Association (ISPAD). DKA was defined according to ISPAD criteria (blood glucose > 11 mmol/L, venous pH < 7.3 or bicarbonate < 15 mmol/L, ketonemia and ketonuria), and severe DKA was categorized as pH < 7.1, bicarbonate < 5 mmol/L (11,12).

Ethics approval was granted by the Ege University Ethics Committee (approval number: 21-6.1T/71, date: 10.04.2016).

Statistical Analysis

All analysis were performed using Statistical Package for the Social Sciences, version 21 (IBM Inc., Chicago, IL, USA). Categorical data are described using observed frequencies and percentages, and continuous variables are summarized as mean and standard deviation. In cases of non-parametric distribution of data, median and interquartile range is used to describe the data set. Patient and control data were compared using chi-square test. A p value < 0.05 was considered to be statistically significant.

Results

Between March 2016 and March 2021, 199 patients were diagnosed with T1DM, of whom 105 (52.7%) were boys. Baseline demographics and characteristics at diagnosis are given in Table 1. The mean age at the time of diagnosis of the patients was 8.4 ± 3.8 years, and ranged from 2 to 18 years.

The rate of DKA at presentation was similar in the COVID-19 group (2020 and 2021) compared to the pre-pandemic

Table 1. Demographics and clinical characteristics at diagnosis of T1DM from March 2016 to March 2020 (control period) and March 2020 to March 2021 (pandemic period)

		2020-2021	2019-2020	2018-2019	2017-2018	2016-2017
New onset diagnosed T1DM	(n)	48	47	33	29	42
Median (range) age at diagnosis (years)		9.4 (0.8-18)	7.0 (1.2-17)	9.8 (1.2-16.5)	9.2 (1.09-16)	9.8 (0.7-15.5)
Age groups n (%); median (range) age (years)	≤5 years	11 (23%); 3.1 (1.1-4.9)	14 (29.8%); 3.2 (2.8- 4.5)	6 (18.2%); 4.3 (4- 4.8)	6 (20.7%); 3.9 (3.2- 4.6)	12 (28.6%); 4.1 (1.7- 4.9)
	5-12 years	19 (39.5%); 8.7 (5.1-11.6)	21 (44.7%); 7.8 (5.2-11.7)	14 (42.4%); 10.3 (5.6-11.7)	14 (48.3%); 9.5 (5.1-11.9)	12 (28.6%); 7.9 (5.1-11.3)
	12-18 years	18 (37.5%); 13.7 (12.2-18)	12 (25.5%); 14.5 (12.1-17.5)	13 (39.4%); 15.4 (12.4-17.5)	9 (31.0%); 15.6 (12.5-18.0)	18 (42.9%); 16.2 (12.4-17.9)
Median (range) duration of symptoms (days)		30 (2-90)	10 (1-90)	10 (1-90)	8.5 (4-90)	20 (0-90)

T1DM: type 1 diabetes mellitus

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control period (2016-2018) (58.3% in 2020 vs 55.3% in 2019, 45.5% in 2018, 44.8% in 2017, 64.3% in 2016, p > 0.05). Although the rate of DKA was similar, the rate of severe DKA in the last 2 years was higher than previous years (30.4% in 2020 and 45.7% in 2019, 24.2% in 2018, 18.5% in 2017, 17.1% in 2016, p = 0.027). Although statistically insignificant, the mean duration of symptoms prior to presentation during the pandemic period was longer than the previous years (p > 0.05) (Table 1).

Discussion

The COVID-19 pandemic has continued since first being declared in early 2019. During the pandemic period, many national health care systems have experienced great difficulties and resources have been stretched. Furthermore, given the fear and uncertainty in the population, especially in the initial period of the pandemic many people postponed doctors appointments and did not attend hospital until complaints had progressed (13,14). The study center for the present study is a tertiary level university hospital with 165,000 outpatients/year. Following the movement restrictions imposed because of the COVID-19 pandemic, services were transferred to online outpatient clinics and only emergencies were accepted.

Delayed diagnosis of T1DM may predispose to DKA and thus DKA incidence may be expected to increase during COVID-19 due to late presentation. Although there is conflicting evidence about whether or not COVID increased the frequency of DKA, it does not seem to have increased the incidence of T1DM during the first 14 months of the pandemic (15,16,17). Ho et al. (18) in a retrospective analysis of 221 new onset T1DM in a single center in Canada, showed no increase in the incidence of T1DM during 2020, compared to 2019.

Zubkiewicz-Kucharska et al. (19) analyzed the incidence of diabetes in the last 20 years from lower Silesia in 1961 new onset T1DM pediatric patients. The incidence of T1DM in children from Lower Silesia during the COVID-19 pandemic was compared with previous years, and their clinical status (incidence of DKA, the mean pH upon at admission) at the time of diagnosis was worse during the pandemic than prior to it. A study from Southeastern Brazil revealed a higher incidence and severity of new onset T1DM cases with DKA during the pandemic period (20). Lawrence et al. (21) compared new onset pediatric T1DM patients during the pandemic to those presenting in the previous 5 years and showed an increased incidence of severe DKA during pandemic period. These authors attributed this to delayed admission as a result of concerns regarding

COVID-19 and the restrictions put in place to combat the COVID-19 pandemic. In the study of Kamrath et al. (22), 532 children with new onset T1DM presenting during the pandemic were examined and the frequency of DKA and severe DKA was 44.7% and 19.4% respectively, which was double that found in the pre-pandemic period (aRR 1.8-2.7 and aRR 1.4-2.1, respectively). Patients in younger age groups exhibited a higher risk of DKA (RR 2.1-2.8). In the present study, the frequency of DKA was 58.3%, while the frequency of severe DKA was 30.4%. Although Turkey imposed had intensive measures aimed at combatting the spread of SARS-CoV-2 and most outpatient clinics were suspended except for emergencies, the incidence of DKA at presentation with newly diagnosed T1DM did not change compared to previous years.

In the present study, the duration of symptoms prior to presentation during the pandemic period was 30 (2-90) days. In the study of Zubkiewicz-Kucharska et al. (19), the mean duration of symptoms was 13.1 ± 10.96 days, which was similar to previous years. In our study, although the duration of symptoms was not statistically significant, was much longer than expected and longer than the previous years (Table 1). The increased frequency of severe DKA, may be due to the delay in accessing health care due to lack of access or fear of COVID-19. Although a one-year period is a relatively short period of time to draw detailed and robust conclusions about the impact of the COVID-19 outbreak, this study showed an increased incidence of severe DKA compared with the three years prior to the pandemic and longer duration of symptoms prior to presentation.

Study Limitations

We did not have data about the presence of antibodies to SARS-CoV-2 or previous COVID-19 infection in the patients with new onset T1DM in the years 2019 and 2020. Furthermore, making estimates of changes in incidence of a relatively rare disease in a small population on a year-to-year basis is somewhat unreliable although trends of clinical significance may be identified.

Conclusion

Although COVID-19 infection does not seem to have increased the incidence of DKA, it is important to encourage knowledge among first-line clinicians about the likelihood of DKA likely to increase during the COVID-19 outbreak. Severe DKA was seen more frequently at the time of diagnosis in children with T1DM diagnosed during the pandemic period, and the duration of hyperglycemia symptoms was longer than in previous years. Delays in diagnosis are possibly due to parental behavior and poor access to healthcare.

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Ethics

Ethics Committee Approval: Ethics approval was granted by the Ege University Ethics Committee (approval number: 21-6.1T/71, date: 10.04.2016).

Informed Consent: Written consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Arzu Jalilova, Damla Gökşen, Design: Şükran Darcan, Damla Gökşen, Data Collection or Processing: Arzu Jalilova, Hafize Işıklar, Analysis or Interpretation: Günay Demir, Samim Özen, Şükran Darcan, Literature Search: Arzu Jalilova, Yasemin Atik Altınok, Writing: Arzu Jalilova, Aysun Ata, Damla Gökşen.

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