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

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Abstract
Introduction: Diabetic ketoacidosis (DKA) is a life-threatening acute complication of type 1 diabetes mellitus (T1DM) and infection is the most common precipitating factor and is responsible for more than 50% of cases. The frequency and severity of diabetic ketoacidosis in children with T1DM, before and during the coronavirus disease 2019 outbreak were evaluated in order to identify its effects on DKA incidence.


Results: The rate of DKA at presentation was similar during the pandemic period compared to the pre-pandemic years (58.3% in 2020 vs 55.3% in 2019, 45.5% in 2018, 44.8% in 2017, 64.3% in 2016, p = 0.393). Although the percentage of DKA was similar, the rate of severe DKA in the last 2 years was higher than previous years. Although statistically insignificant, 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 COVID-19 pandemic and lock-down compared to the prior 4 years. This may be mainly due to the behavior of the parents of sick children and effectiveness of healthcare system. Despite many road-blocks due to overburden of healthcare system during COVID-19 pandemic, parents might have been concern enough to seek medical attention for their children, avoiding increased frequency of DKA at the first presentation of new-onset T1DM.

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

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Introduction
T1D is characterized by chronic immune-mediated destruction of pancreatic β cells leading to partial or absolute insulin deficiency. In the majority of cases, it results from autoimmune-mediated pancreatic β-cell destruction and is influenced by different factors such as genes, age, and ethnicity. 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. These infections may trigger acute complications of T1DM including DKA and in some occasions, hypoglycemia. In medical literature there are reports about the relation between fulminant picture of DM and different infections, but such reports about SARS-CoV-2 infection are rare. Infection is usually a precipitating factor of DKA and is responsible for more than half of the cases. Pancreatic beta cell function may deteriorate after COVID-19, and it may trigger DKA in diabetic patients. The aim of this study was to determine the clinical characteristics and frequency of diabetic ketoacidosis (DKA) in children diagnosed with T1DM during the COVID-19 outbreak and to compare it with previous years.

Methods
The study population included children less than 18 years of age presenting with a 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 those new onset T1DM from March 2016 to March 2020.

Ethics approval was granted by the Ege University Ethics Committee (approval number: 21-6.1.171) Patients with syndromic diabetes, type II diabetes, maturity onset diabetes in the young, secondary diabetes (cystic fibrosis, steroid use and lipodystrophy, etc.) were excluded from the study. Patient data were analyzed by the retrospective review of medical records. The cases were diagnosed as 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.

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

Results
From March 2016 to March 2021, 199 patients were diagnosed as T1DM (105 boys (52.7%) and 94 girls (47.4%). Baseline demographics and characteristics at diagnosis are given in table 1. The mean age of the patients were 8.4 ± 3.8 years (2–18 yrs). 52 % of the patients had symptoms for at least 4 weeks during the 19 Covid period and 30 % during pre-pandemic period (p=0.05).

The rate of DKA at presentation was similar during the pandemic period compared to the pre-pandemic control period (58.3% in 2020 vs 55.3% in 2019, 45.5% in 2018, 44.8% in 2017, 64.3% in 2016, p =0.393).). 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 vs 45.7% in 2019, 24.2% in 2018, 18.5% in 2017, 17.1% in 2016, p =0.027). The duration of symptoms were longer in the COVID-19 period than the previous years (p=0.05).

Discussion
More than a year has passed since the onset of the COVID-19 pandemic. During the pandemic period, many countries had difficulties in the health care systems, many hospitals were reorganized as covid hospitals, many intensive care units exceeded their capacity, many outpatient ...
clinics were closed or limited the number of patients, many people postponed their doctor's applications and did not refer before their complaints progressed. Our hospital is a tertiary university hospital with 165 000 outpatients/year. With the COVID-19 pandemic, outpatient care unit moved to online format where only emergencies were accepted. Although such a move may delay diagnosis, treatment started in time and patients' conditions improved. In conclusion, timely diagnosis and treatment in our hospital is due to parents' cooperation and access to healthcare. In children with T1D diagnosed during the pandemic period, and the duration of diabetes was longer than in previous years. Delays in diagnosis are likely due to parental behavior and access to healthcare.

Conflict of Interest
None of the authors have any potential conflicts of interest associated with this research.

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Disclosures
All the authors accepted responsibility for the entire content of this submitted manuscript and approved submission. Informed Consent: Written consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Approval date of Registry and the Registration No. Ethics approval was granted by the Ege University Ethics Committee (approval number: 21-6.17/71)

Animal Studies: N/A

References

Table 1. Demographics and clinical characteristics at diagnosis of DM1 from March 2016 to March 2020 (control period) and March 2020 to March 2021 (pandemic period)

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<tbody>
<tr>
<td>Age at diagnosis (years)</td>
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<tr>
<td>Median (min-max)</td>
<td>9.4 (0.8-18)</td>
<td>7.0 (1.2-17)</td>
<td>9.8 (1.2-16.5)</td>
<td>9.2 (1.09-16)</td>
<td>9.8 (0.7-15.5)</td>
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<td>Age group (n)</td>
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<td>≤ 5 years</td>
<td>11 (23.4%)</td>
<td>14 (30.4%)</td>
<td>6 (18.2%)</td>
<td>6 (20.7%)</td>
<td>12 (28.6%)</td>
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<td>Median (min-max)</td>
<td>3.2 (1.1-4.9)</td>
<td>4.3 (4.4-8)</td>
<td>3.9 (3.2-4.6)</td>
<td>4.1 (1.7-4.9)</td>
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<td>5-12 years</td>
<td>19 (40.4%)</td>
<td>21 (45.7%)</td>
<td>14 (42.4%)</td>
<td>14 (48.3%)</td>
<td>12 (28.6%)</td>
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<tr>
<td>Median (min-max)</td>
<td>8.7 (5.1-11.6)</td>
<td>7.8 (5.6-11.7)</td>
<td>10.3 (5.6-11.7)</td>
<td>9.5 (5.1-11.9)</td>
<td>7.9 (5.1-11.3)</td>
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<td>12-18 years</td>
<td>17 (36.2%)</td>
<td>11 (23.9%)</td>
<td>13 (39.4%)</td>
<td>9 (31.0%)</td>
<td>18 (42.9%)</td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>13.7 (12.2-18)</td>
<td>14.5 (12.1-17.5)</td>
<td>15.4 (12.4-17.5)</td>
<td>15.6 (12.5-18.0)</td>
<td>16.2 (12.4-17.9)</td>
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<td>Duration of Symptoms (day)</td>
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<tr>
<td>Median (min-max)</td>
<td>30 (2-365)</td>
<td>10 (1-365)</td>
<td>10 (1-120)</td>
<td>8.5 (4-90)</td>
<td>20 (0-360)</td>
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