ORIGINAL ARTICLE

A Long-Term Comparison of Presenting Characteristics of Children with Newly Diagnosed Type 1 Diabetes Before and During the COVID-19 Pandemic

🆔 Gülay Kaya[1], 🆔 Emine Ayça Cimbek[2], 🆔 Osman Yeşilbaş[3], 🆔 Yusuf Emre Bostan[4], 🆔 Gülay Karagüzel[2]

[1]Karadeniz Technical University Faculty of Medicine, Department of Pediatrics, Trabzon, Turkey
[2]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Endocrinology, Trabzon, Turkey
[3]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Intensive Care, Trabzon, Turkey
[4]Karadeniz Technical University Faculty of Medicine, Department of Public Health, Trabzon, Turkey

What is already known on this topic?

The limited use of healthcare services due to fear of Coronavirus disease-2019 (COVID-19) transmission during the pandemic has raised concerns of delays in type 1 diabetes mellitus (T1D) diagnosis, among other diseases. This study investigates the presenting characteristics of newly diagnosed T1D patients assessed in our clinic during the pandemic and compares them with the pre-pandemic period.

What this study adds?

We observed an increased frequency and severity of diabetic ketoacidosis in children with newly diagnosed T1D in the pandemic period. Our study provides an additional contribution to the literature in its coverage of the one-year period during the pandemic and its comparison with the previous three years.

Abstract

Objective: Diabetic ketoacidosis (DKA) - a potentially preventable complication of type 1 diabetes mellitus (T1D) - is one of the most common chronic childhood diseases, and is associated with a significant risk of morbidity and mortality. The limited use of healthcare services due to fear of Coronavirus disease-2019 (COVID-19) transmission during the pandemic has raised concerns of delays in T1D diagnosis, among other diseases. This study investigated the presenting characteristics of newly diagnosed T1D patients assessed in a single clinic during the pandemic and compares them with the pre-pandemic period.

Methods: For the purpose of this study, the first year of the pandemic is referred to as the "pandemic period", and the previous three years as the "pre-pandemic period". Patient files were reviewed retrospectively, the demographic and clinical characteristics and laboratory findings of the patients were recorded, and the findings from both periods were compared.

Results: The number of patients diagnosed with T1D in the pandemic period was 44, and in the pre-pandemic period 39 in 2017, 22 in 2018 and 18 in 2019. The two groups had similar age, sex, pubertal stage and anthropometric characteristics (p > 0.05). Regarding the type of presentation, the frequency of DKA was significantly higher in the pandemic period (68.2%) than in the pre-pandemic period (40.5%) (p = 0.006), and this difference was also observed in the comparison by years (p = 0.016). The duration of symptoms (16.5 ± 10.7 vs. 23.5 ± 17.6 days) and the length of hospital stay (10 ± 3.9 vs. 15.2 ± 5.5 days) were significantly shorter in the pandemic period (p = 0.032, and p < 0.001, respectively). There was no difference in the frequency of severe DKA between the pandemic (46.7%) and the pre-pandemic (37.5%) periods (p > 0.05). However, pH (7.17 ± 0.16 vs. 7.26 ± 0.14) and bicarbonate (12.8 ± 6.3 vs. 16.6 ± 6.3) levels were significantly lower in the pandemic period (p < 0.005). Additional signs of infection on admission were less frequent in the pandemic period (9.1%) than in the pre-pandemic period (27.8%) (p = 0.027). The groups did not differ in terms of hemoglobin A1c, C-peptide, concurrent thyroid autoantibodies and tissue transglutaminase antibodies (p > 0.05). The rate of anti-glutamic acid decarboxylase positivity was higher in the pandemic period (73.8% vs. 39.2%) (p = 0.001) while the frequency of other diabetes-

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

associated autoantibodies was similar between the groups (p > 0.05). The polymerase chain reaction test for COVID-19 was negative in six patients with a history of contact.

Conclusion: There was an increased frequency and severity of DKA in children with newly diagnosed T1D in the pandemic period, and these findings justify concerns related to the diagnosis of other diseases during the pandemic. Studies to raise awareness of diabetes symptoms during the pandemic should be continued regularly to reach all segments of society. Our study provides an additional contribution to the literature in its coverage of the one-year period during the pandemic and its comparison with the previous three years.

Keywords: COVID-19, type-1 diabetes, diabetic ketoacidosis, child

Introduction

The novel Coronavirus disease-2019 (COVID-19) caused by the Severe acute respiratory syndrome-Coronavirus-2 virus was first reported in late 2019 in Wuhan in the Hubei province of China (1). The virus spread rapidly all over the world, and the World Health Organization and the Center for Disease Control and Prevention declared COVID-19 a pandemic on March 24, 2020 (2). The first case of COVID-19 in Turkey was reported on March 11, 2020 (3). Most of the hospitals in Turkey were assigned as referral hospitals, so that most were affected by postponement of outpatient appointments. In the first year of the pandemic, Turkey imposed social distancing restrictions from time to time to varying degrees (3). The limited use of healthcare services and the fear of contracting COVID-19 infection in hospitals have led to concerns about delays in the diagnosis of serious diseases.

The early diagnosis of type-1 diabetes mellitus (T1D) and establishment of metabolic control are known to prevent many of the associated acute complications. T1D patients mostly present with symptoms such as polyuria, polydipsia, enuresis and weight loss (4). Diabetic ketoacidosis (DKA) is the most severe, life-threatening, acute complication of T1D. At the onset of newly diagnosed T1D in childhood, the reported frequency of DKA is 15-70% in various regions around the world (5).

The increased presentation of severe DKA among children in the diagnosis of T1D during the COVID-19 pandemic is a major concern. Severe DKA is not only life-threatening but also leads to the use of intensive care beds and resources during a period of potentially high demand. The limited studies of this issue conducted during the pandemic report different findings regarding the frequency of DKA on admission (6,7,8,9,10,11,12,13). The present study compares the clinical and laboratory characteristics of pediatric patients with newly diagnosed T1D during the pandemic with those of the three pre-pandemic years to identify factors affecting the results, and makes recommendations in this regard.

Methods

This study included newly diagnosed T1D patients aged 0-18 years who were followed up in the Pediatric Endocrinology Clinic and Pediatric Intensive Care Unit of the Karadeniz Technical University Faculty of Medicine. The collected data were analyzed in two groups. For the purpose of this study, the first year of the pandemic (February 1, 2020-January 31, 2021) was considered the "pandemic period" and the previous three years (February 1, 2019-January 31, 2020; February 1, 2018-January 31, 2019; and February 1, 2017-January 31, 2018) were considered the "pre-pandemic period". A retrospective review was made of the file records of the patients, comparing the age and date of diagnosis, sex, family history of diabetes, symptoms on admission to the outpatient clinic (polyuria, polydipsia, enuresis, vomiting, altered consciousness, fever, signs of infection, increased appetite, weight loss, Kussmaul breathing), duration of symptoms, body weight, body mass index (BMI) [BMI = (kg)/height (m^2)], pubertal status, venous blood gas [pH, partial pressure of carbon dioxide (pCO$_2$), bicarbonate (HCO$_3$)], hemogram, biochemistry [glucose, blood urea nitrogen, creatinine, corrected sodium, potassium, chloride, amylase, calcium, phosphorus, alkaline phosphatase], hemoglobin A1c (HbA1c), preprandial-postprandial C-peptide, 25-hydroxyvitamin D [25(OH)D], parathormone (PTH), insulin autoantibodies (IAA), islet-cell antibodies (ICA), glutamic acid decarboxylase antibodies (anti-GAD), anti-tissue transglutaminase antibodies, thyroid function tests [tyroid stimulating hormone (TSH), fT3, fT4], anti-thyroid peroxidase (TPO), anti-thyroglobulin (anti-TG) antibodies and length of hospital stay.

HbA1c was measured by spectrophotometric method, and C-peptide levels were estimated by electrochemiluminescence (ECLIA)-(VARIANT II, IMMULITE® 2000 XPi). The presence of IAA, ICA, and GADA was determined by chemiluminescence immunoassay-(SNIBE MAGLUMI). The ECLIA method was used to analyze PTH, 25(OH)D, TSH, fT3, fT4, TPO and anti-TG.

DKA was diagnosed and classified at the time of admission in accordance with the ISPAD 2018 guidelines (5). In contrast

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

to earlier studies, the present study also included cases with a history and clinical presentation compatible with T1D, but without positive diabetes-associated autoantibodies. Patients with positive IAA, ICA or anti-GAD were classified as type 1a while antibody-negative patients were classified as type 1b. Cases with a random blood glucose value of > 200 mg/dL, pH of < 7.30 and HCO_3 of < 15 mmol/L in blood gas, and positive urine ketones in a urine analysis were considered DKA. Patients diagnosed with DKA were divided into mild, moderate and severe groups according to their blood gas results. Cases with a blood gas pH of < 7.3 or HCO_3 of < 15 mmol/L were considered mild DKA, while a pH of < 7.2 or HCO_3 of < 10 mmol/L indicated moderate DKA and a pH of < 7.1 or HCO_3 of < 5 mmol/L indicated severe DKA (5).

The study was initiated upon the written approval by the Clinical Research Ethics Committee of Karadeniz Technical University Faculty of Medicine (protocol number: 2021/210, date: 07.09.2021).

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences for Windows, version 23.0 (IBM Inc., Armonk, NY, USA). Descriptive statistics are presented as numbers and percentages for categorical variables, and mean, standard deviation, minimum and maximum for quantitative variables. A Kolmogorov-Smirnov test was used to test the normality of continuous variables; quantitative variables were compared between two independent groups using the Student's t-test or the Mann-Whitney U test; and differences in the rates of categorical variables were analyzed using a chi-square test. The level of statistical significance (alpha) was $p < 0.05$. A Fisher's exact test and an ANOVA were used to analyze the differences between the pandemic and pre-pandemic groups.

Results

In total, the records of 123 newly diagnosed T1D were included in the study. The number of patients with newly diagnosed T1D was higher in the pandemic period (44) than in the three pre-pandemic years (39, 22 and 19, respectively). Demographic, clinical and laboratory data of the groups according to the pre-pandemic-pandemic period and years are presented in Tables 1 and 2. Autoantibody data of pre-pandemic period and pandemic period groups are presented in Table 3. The age, sex, pubertal stage and anthropometric characteristics of the groups were similar ($p > 0.05$). Regarding the type of presentation, the frequency of DKA was significantly higher in the pandemic period (68.2%) than in the

pre-pandemic period (40.5%) ($p = 0.006$), and the difference in the frequency of DKA was also observed in a comparison by year ($p = 0.016$). The duration of symptoms (16.5 ± 10.7 vs. 23.5 ± 17.6 days) and the length of hospital stay (10.0 ± 3.9 vs. 15.2 ± 5.5 days) were shorter in the pandemic period ($p = 0.032$ and $p < 0.001$, respectively). There was no difference in the frequency of severe DKA between the pandemic (46.7%) and the pre-pandemic (37.5%) periods ($p > 0.05$). However, the pH (7.1 ± 0.1 vs. 7.26 ± 0.1) and bicarbonate (12.8 ± 6.3 and 16.6 ± 6.3) levels were significantly lower in the pandemic period ($p < 0.005$). Additional signs of infection (mostly tonsillitis) on admission were less frequent in the pandemic period (9.1%) than in the pre-pandemic period (27.8%) ($p = 0.027$). The groups did not differ in terms of HbA1c, C-peptide, and frequency of concurrent thyroid autoantibodies and tissue transglutaminase antibodies ($p > 0.05$). The rate of anti-GAD positivity was higher in the pandemic period (73.8% vs. 39.2%) ($p = 0.001$) while the frequency of other diabetes-associated autoantibodies was similar between the groups ($p > 0.05$).

Furthermore, 17 of the 40 (42.5%) patients in the pandemic period, and a similar proportion of 28 of the 75 (37.3%) patients in the pre-pandemic period had a 25(OH)D level of < 15 μg/L while 23 of the 40 (57.5%) patients in the pandemic period and 47 of the 75 (62%) patients in the pre-pandemic period had a 25(OH)D level of < 20 μg/L. Polymerase chain reaction (PCR) tests were performed in six patients with a history of contact, revealing no COVID-19-positive case.

Discussion

In this study the number of patients with newly diagnosed T1D was higher in the pandemic period than in each of the three pre-pandemic years. The incidence of T1D worldwide has been increasing over the recent years (4). In addition, only one other hospital has a Pediatric Endocrinology Clinic in our city. As that hospital worked as a pandemic hospital during the study period, all patients with T1D were referred to our center, which is the reference hospital. This may explain the higher number of patients during the pandemic period than the pre-pandemic period.

In the present study, significant increases were identified in the frequency (68.2% vs. 40.5%) of children presenting with DKA, the severity of DKA [(pH: 7.17 ± 0.16 vs. 7.26 ± 0.14), and bicarbonate levels (12.8 ± 6.3 vs. 16.6 ± 6.3)] at the onset of newly diagnosed T1D during the COVID-19 pandemic when compared to the pre-pandemic period. While the frequency of severe DKA increased in the pandemic period

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

when compared to the pre-pandemic period, the difference was not significant (46.7% vs. 37.5%).

The results of other studies conducted during the COVID-19 pandemic regarding DKA and severe DKA in children with T1D at the time of diagnosis are consistent with our findings. A previous study of Canadian children found the presentation of DKA to be higher during the pandemic

than in the pre-pandemic period (55% vs. 36.4%), and the same study also established an increased presentation of hospital admissions with severe DKA (48.3% vs. 33.3%) (6). In Australia, a study reported the frequency of DKA in children to be significantly higher during the pandemic than in the pre-pandemic period (73% vs. 26%), and again, the results on the frequency of severe DKA were similar (45%

Table 1. Demographic, clinical and laboratory results of pre-pandemic and pandemic patients

	Pre-pandemic period n = 79	Pandemic period n = 44	Total	p
Age at T1D onset (years)	8.13 ± 4.75	8.48 ± 4.37	8.26 ± 4.60	0.572
Sex				1.000
Female	46.8% (37)	45.5% (20)	46.3% (57)	
Male	53.2% (42)	54.5% (24)	53.7% (66)	
Pubertal stage				
Prepubertal	69.6% (55)	59.1% (26)	65.9% (81)	
Pubertal	30.4% (24)	40.9% (18)	34.1% (42)	0.326
Weight SDS	-0.15 ± 1.32 (79)	-0.10 ± 1.28 (44)	-0.13 ± 1.30 (123)	0.852
Height SDS	0.39 ± 1.44 (79)	0.49 ± 1.12 (44)	0.42 ± 1.33 (123)	0.681
BMI SDS	-0.51 ± 1.72 (79)	-0.63 ± 1.55 (44)	-0.55 ± 1.66 (123)	0.724
Family history				
Negative	81.0% (64)	79.5% (35)	80.5% (99)	1.000
Positive	19.0% (15)	20.5% (9)	19.5% (24)	
Duration of symptoms (days)	23.51 ± 17.60 (79)	16.54 ± 10.73 (44)	21.02 ± 15.81 (123)	**0.032**
Hospitalization duration (days)	15.20 ± 5.53 (79)	10.02 ± 3.89 (44)	13.35 ± 5.58 (123)	**0.000**
Additional infections*				
Negative	72.2% (57)	90.9% (40)	78.9% (97)	**0.027**
Positive	27.8% (22)	9.1% (4)	21.1% (26)	
DKA at presentation				
No DKA	59.5% (47)	31.8% (14)	49.6% (62)	**0.006**
DKA	40.5% (32)	68.2% (30)	50.4% (61)	
Presentations by severity				
Mild DKA	37.5% (12)	36.7% (11)	37.1% (23)	
Moderate DKA	25.0% (8)	16.7% (5)	21.0% (13)	0.662
Severe DKA	37.5% (12)	46.7% (14)	41.9% (26)	
Creatinine (mg/dL)	0.56 ± 0.18 (79)	0.56 ± 0.18 (44)	0.56 ± 0.18 (123)	0.920
Calcium (mg/dL)	9.57 ± 0.57 (79)	9.51 ± 0.46 (42)	9.55 ± 0.53 (121)	0.583
Phosphorus (mg/dL)	4.33 ± 1.22 (79)	4.34 ± 0.74 (43)	4.33 ± 1.07 (122)	0.626
ALP (U/L)	245.73 ± 126.40 (74)	202.65 ± 78.69 (41)	230.37 ± 113.28 (115)	0.070
25(OH)D (μg/L)	19.00 ± 10.12 (75)	17.36 ± 9.11 (40)	18.43 ± 9.77 (115)	0.538
PTH (ng/L)	20.44 ± 13.00 (75)	25.00 ± 15.68 (41)	22.11 ± 14.14 (112)	0.101
TSH (mIU/L)	2.77 ± 1.73 (79)	2.61 ± 1.74 (43)	2.71 ± 1.73 (122)	0.635
fT4 (ng/L)	1.08 ± 0.32 (79)	1.03 ± 0.57 (43)	1.06 ± 0.42 (122)	0.179
fT3 (ng/dL)	3.16 ± 0.82 (52)	3.35 ± 0.99 (36)	3.24 ± 0.90 (88)	0.306
pH	7.26 ± 0.14 (78)	7.17 ± 0.16 (44)	7.23 ± 0.15 (122)	**0.002**
PCO_2	31.20 ± 10.88 (78)	25.95 ± 10.28 (43)	29.33 ± 10.92 (121)	**0.010**
HCO_3 (mmol/L)	16.62 ± 6.30 (78)	12.77 ± 6.28 (44)	15.23 ± 6.53 (122)	**0.003**
HbA1c (%)	11.91 ± 2.60 (79)	12.26 ± 2.57 (43)	12.03 ± 2.58 (122)	0.479
Preprandial C-peptide (μg/L)	0.42 ± 0.40 (77)	0.81 ± 2.73 (42)	0.56 ± 1.65 (119)	0.736
Postprandial C-peptide (μg/L)	0.68 ± 0.60 (69)	0.62 ± 0.56 (37)	0.66 ± 0.58 (106)	0.464

*Additional infections: 70% tonsillitis.
BMI: body mass index, DKA: diabetic ketoacidosis, ALP: alkaline phosphatase, 25(OH)D: 25-hydroxyvitamin D, PTH: parathormone, TSH: tyroid stimulating hormone, pCO_2: partial pressure of carbon dioxide, HCO_3: bicarbonate, HbA1c: hemoglobin A1c, SDS: standard deviation score, fT3: free triiodothyronine, fT4: free thyroxine

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

vs. 5%) (7). In a study from Germany, an increase in DKA (23.5% vs. 44.7%) and severe DKA (13.9% vs. 19.7%) were identified during the COVID-19 pandemic, with those under the age of 6 years being at greater risk (8). A study of children in the United Kingdom reported a high rate (70%) of children presenting with DKA during the pandemic, with severe DKA being identified in more than half (52%) (9). In contrast, a study from Poland reported no increase in DKA during the pandemic when compared to the previous year, but identified an increased frequency of severe DKA (10). A multicenter study of children in Saudi Arabia reported a higher rate of DKA in those newly diagnosed with T1D during the pandemic (26%) compared to the pre-pandemic year (13.4%), with the frequency of severe DKA being similar in both years (11). In a study from Italy, fewer pediatric cases of newly diagnosed T1D (23%) but an increased frequency

Table 2. Demographic, clinical and laboratory results of patients by years

	2017 (n = 39)	2018 (n = 22)	2019 (n = 18)	2020 (n = 44)	Total (n = 123)	p
Age at T1D onset (years)	7.57 ± 4.40	8.52 ± 4.88	8.85 ± 5.42	8.48 ± 4.37	8.26 ± 4.60	0.778
Sex						0.848
Female	51.3% (20)	45.5% (10)	38.9% (7)	45.5% (20)	46.3% (57)	
Male	48.7% (19)	54.5% (12)	61.1% (11)	54.5% (24)	53.7% (66)	
Pubertal stage						0.355
Prepubertal	76.9% (30)	63.6% (14)	61.1% (11)	59.1% (26)	65.9% (81)	
Pubertal	23.1% (9)	36.4% (8)	38.9% (7)	40.9% (18)	34.1% (42)	
Height SDS	0.17 ± 1.39	-0.36 ± 1.23	-0.58 ± 1.16	-0.10 ± 1.28	-0.13 ± 1.30	0.168
Weight SDS	0.65 ± 1.20	0.11 ± 1.68	0.15 ± 1.57	0.49 ± 1.12	0.42 ± 1.33	0.351
BMI SDS	-0.30 ± 1.56	-0.57 ± 1.60	-0.90 ± 2.19	-0.63 ± 1.55	-0.55 ± 1.66	0.636
Family history						
Negative	92.3% (36)	81.8% (18)	55.6% (10)	79.5% (35)	80.5% (99)	
Positive	7.7% (3)	18.2% (4)	44.4% (8)	20.5% (9)	19.5% (24)	
Duration of symptoms (days)	25.69 ± 20.25	20.72 ± 15.97	22.22 ± 12.97	16.54 ± 10.73	21.02 ± 15.81	0.143
Hospitalization duration (days)	14.84 ± 5.69	15.59 ± 5.41	15.50 ± 5.61	10.02 ± 3.89	13.35 ± 5.58	**0.000**
Additional infections*						
Negative	69.2% (27)	77.3% (17)	72.2% (13)	90.9% (40)	78.9% (97)	
Positive	30.8% (12)	22.7% (5)	27.8% (5)	9.1% (4)	21.1% (26)	
DKA at presentation						
No DKA	66.7% (26)	50.0% (11)	55.6% (10)	31.8% (14)	49.6% (61)	**0.016**
DKA	33.3% (13)	50.0% (11)	44.4% (8)	68.2% (30)	50.4% (62)	
Presentations by severity						
Mild DKA	23.1% (3)	27.3% (3)	75.0% (6)	36.7% (11)	37.1% (23)	
Moderate DKA	15.4% (2)	36.4% (4)	25.0% (2)	16.7% (5)	21.0% (13)	
Severe DKA	61.5% (8)	36.4% (4)	0.0% (0)	46.7% (14)	41.9% (26)	
Creatinine (mg/dL)	0.58 ± 0.18	0.55 ± 0.16	0.52 ± 0.19	0.56 ± 0.18	0.56 ± 0.18	0.616
Calcium (mg/dL)	9.54 ± 0.53	9.69 ± 0.59	9.50 ± 0.64	9.51 ± 0.46	9.55 ± 0.53	0.470
Phosphorus (mg/dL)	4.31 ± 0.93	4.36 ± 0.97	4,36 ± 1.93	4.34 ± 0.74	4.33 ± 1.07	0.770
ALP (U/L)	249.74 ± 131.65	260.72 ± 135.25	218.05 ± 104.39	202.65 ± 78.69	230.37 ± 113.28	0.191
25(OH)D (µg/L)	19.85 ± 10.60	18.01 ± 11.71	18.30 ± 6.42	17.36 ± 9.11	18.43 ± 9.77	0.598
PTH (ng/L)	23.32 ± 11.13	17.03 ± 17.05	19.22 ± 8.95	25.00 ± 15.68	22.11 ± 14.14	**0.040**
TSH (mIU/L)	2.81 ± 1.50	2.73 ± 2.35	2.71 ± 1.38	2.61 ± 1.74	2.71 ± 1.73	0.733
fT4 (ng/L)	1.13 ± 0.32	0.96 ± 0.27	1.11 ± 0.35	1.03 ± 0.57	1.06 ± 0.45	0.141
fT3 (ng/dL)	3.55 ± 0.73	2.78 ± 0.84	2.91 ± 0.69	3.35 ± 0.99	3.24 ± 0.90	**0.018**
pH	7.27 ± 0.15	7.22 ± 0.16	7.29 ± 0.07	7.17 ± 0.16	7.23 ± 0.15	**0.008**
pCO_2	31.12 ± 10.74	29.01 ± 11.68	33.92 ± 10.20	25.95 ± 10.28	29.33 ± 10.92	**0.030**
HCO_3 (mmol/L)	17.07 ± 6.58	15.16 ± 6.67	17.36 ± 5.18	12.77 ± 6.28	15.23 ± 6.53	**0.014**
HbA1c (%)	11.74 ± 2.69	12.32 ± 2.59	11.75 ± 2.50	12.26 ± 2.57	12.03 ± 2.58	0.735
Preprandial C-peptide (µg/L)	0.43 ± 0.34	0.49 ± 0.59	0.34 ± 0.23	0.81 ± 2.73	0.56 ± 1.65	0.923
Postprandial C-peptide (µg/L)	0.71 ± 0.56	0.69 ± 0.75	0.64 ± 0.49	0.62 ± 0.56	0.66 ± 0.58	0.766

*Additional infections: 70% tonsillitis.
BMI: body mass index, DKA: diabetic ketoacidosis, ALP: alkaline phosphatase, 25(OH)D: 25-hydroxyvitamin D, PTH: parathormone, TSH: tyroid stimulating hormone, pCO_2: partial pressure of carbon dioxide, HCO_3: bicarbonate, HbA1c: hemoglobin A1c, SDS: standard deviation score, fT3: free triiodothyronine, fT4: free thyroxine

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

of severe DKA were reported during the pandemic when compared to the same period the previous year (44.3% vs. 36%) (12). A study in Turkey reported the rate of DKA in children with newly diagnosed T1D to be higher during the pandemic (91.9%) than in the pre-pandemic year (58.7%), while the frequency of severe DKA was similar in both years (13).

Compared to the pre-pandemic period, the pH and bicarbonate levels on admission were significantly decreased during the pandemic, in line with the increased frequency of DKA. In contrast, there was no statistically significant increase in the frequency of severe DKA. Social isolation and fear of exposure to COVID-19 might have led families to hesitate in referring to hospitals. Although there are currently reduced pandemic restrictions, the pandemic continues, highlighting the significance of our findings.

In newly diagnosed T1D, the risk factors for DKA on admission include age < 2 years, ethnic minority, low BMI, delayed diagnosis and low socioeconomic status, while the presence of a first-degree relative with T1D, a parent with a high level of education and a high incidence of T1D in the community are protective factors (14,15,16). No difference in anthropometric characteristics or the presence of T1D in relatives was identified between the pandemic and pre-pandemic groups in the present study, although the duration of baseline symptoms was found to be shorter in the pandemic period than in the pre-pandemic period (16.5 ± 10.7 vs. 23.5 ± 17.6 days). Similarly, Dżygało et al.

(10) also identified no significant difference in the family history of T1D between the pandemic and pre-pandemic groups. A previous study from the United Kingdom reported a short duration of symptoms with an increased frequency of severe DKA during the pandemic (9), which may be attributed to the fact that the parents were unaware of the typical symptoms of hyperglycemia during the lockdown restrictions.

Although there is a lack of data about additional infections on admission, the rate of additional infections was lower in the pandemic period than in the pre-pandemic period in the present study (9.1% vs. 27.8%). In Turkey, school education was provided through distance learning during the pandemic, except for certain age groups. Previous studies reported a decrease in the incidence of respiratory syncytial virus, parainfluenza viruses, human metapneumovirus, enteroviruses, adenoviruses and influenza viruses during the pandemic in Europe and Australia when compared to the previous years (17,18). We believe that during the pandemic, children were less exposed to infections due to the need to wear masks, the greater attention paid to hygiene, the limitations on social interactions and the closure of schools during lockdown.

In the present study, the rate of anti-GAD positivity was higher in the pandemic period than in the pre-pandemic period (73.8% vs. 39.2%), and similarly, Dilek et al. (13) reported a higher rate of anti-GAD positivity in the pandemic period than in the pre-pandemic period (45.9% vs. 19.6%). Anti-

Table 3. Autoantibody results of pre-pandemic and pandemic-period patients

	Pre-pandemic period % n = 79	Pandemic period % n = 44	Total	p
ICA				0.546
Negative	35.4 (28)	42.9 (18)	38.0 (46)	
Positive	64.6 (51)	57.1 (24)	62.0 (75)	
Anti-GAD				**0.001**
Negative	60.8 (48)	26.2 (11)	48.8 (56)	
Positive	39.2 (31)	73.8 (31)	51.2 (62)	
IAA				0.213
Negative	87.3 (69)	95.2 (40)	90.1 (109)	
Positive	12.7 (10)	4.8 (2)	9.9 (12)	
Anti-TPO				1.000
Negative	87.2 (68)	88.1 (37)	87.5 (105)	
Positive	12.8 (10)	11.9 (5)	12.5 (15)	
Anti-TG				1.000
Negative	97.3 (71)	97.6 (40)	97.4 (111)	
Positive	2.7 (2)	2.4 (1)	2.6 (3)	
Anti-tTGA				0.108
Negative	93.2 (69)	82.5 (33)	89.5 (102)	
Positive	6.8 (5)	17.5 (7)	10.5 (12)	
Type 1b	26.6 (21)	14.3 (6)	22.3 (27)	0.188
Type 1a	73.4 (58)	85.7 (36)	77.7 (36)	

ICA: islet cell autoantibody, IAA: insulin autoantibody, anti-GAD: glutamic acid decarboxylase antibodies, anti-TPO: anti-thyroid peroxidase, anti-TG: anti-thyroglobulin, anti-tTGA: anti-tissue transglutaminase antibodies, type 1a: positive diabetes-associated autoantibodies, type 1b: negative diabetes-associated autoantibodies

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

GAD positivity was found to be a risk factor for autoimmune type-1 diabetes in young children of families exposed to psychosocial stress factors (19). The inability to go to school at all and the limitations on social interactions during the pandemic can be interpreted as psychosocial stress factors. We believe that more detailed studies are required to better clarify the relationship between COVID-19 and anti-GAD positivity.

The length of hospital stay was shorter in the pandemic period than in the pre-pandemic period (10 ± 3.9 vs. 15.2 ± 5.5 days), which is a natural consequence of the fact that most hospitals were assigned as referral hospitals, and beds were reserved mostly for COVID-19 patients during the pandemic.

It has been reported that vitamin D deficiency is common at onset of T1D in children (20). In our study, 42.5% of the 40 patients in the pandemic period, and similarly 37.3% of the 75 patients in the pre-pandemic period had 25(OH)D level < 15 µg/L and 57.5% of the patients in the pandemic period and 62% of the patients in the pre-pandemic period had a 25(OH)D level < 20 µg/L. We found no evidence of increased frequency of vitamin D deficiency or insufficiency associated with inadequate outdoor activities and reduced sunlight exposure due to pandemic restrictions in children with T1D. We could not find any other study examining the frequency of vitamin D deficiency or insufficiency during the COVID-19 pandemic in T1D children.

Study Limitations

Our work has some limitations and strengths. It adds to the limited existing literature describing DKA frequency in children during the COVID-19 pandemic. Moreover, while most of the studies conducted during the pandemic included short-term (average three-month) comparisons, our study covered a one-year period during the pandemic and compared the findings with those of the previous three years, making an additional longer term contribution to literature. The main limitation of our study is that it is a single-center study. However, our center provides care for all children with T1D over a large geographic region, being a reference center. We also could not perform PCR testing for COVID-19 on all patients participating in the study due to the absence of associated symptoms.

Conclusion

In conclusion, we observed an increased frequency and severity of DKA in children with newly diagnosed T1D in the pandemic period. Our findings justify the concerns about the diagnosis of other diseases during the pandemic. To enhance physician and social awareness of T1D symptoms during the pandemic, diabetes awareness campaigns should be continued to reach all segments of society.

References

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in wuhan China: the mystery and the miracle. J Med Virol 2020;92:401-402. Epub 2020 Feb 12

2. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID- 19). Int J Surg 2020;76:71-76. Epub 2020 Feb 26

3. Republic of Turkish Ministry of Health Covid-19 Information page. General Coronavirus Table. Last accessed date: 15 Apr 2021. Available from: https://covid19.saglik.gov.tr/EN-69532/general-coronavirus-table.html

4. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, Aschner P, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl 27):7-19.

5. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, Sperling MA, Codner E. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19(Suppl 27):155-177.

6. Sellers EAC, Pacaud D. Diabetic ketoacidosis at presentation of type 1 diabetes in children in Canada during the COVID-19 pandemic. Paediatr Child Health 2021;26:208-209.

7. Lawrence C, Seckold R, Smart C, King BR, Howley P, Feltrin R, Smith TA, Roy R, Lopez P. Increased paediatric presentations of severe diabetic ketoacidosisin an Australian tertiary centre during the COVID-19 pandemic. Diabet Med 2021;38:e14417. Epub 2020 Oct 23

Kaya G et al.
Type 1 Diabetes Before and During the COVID-19 Pandemic

J Clin Res Pediatr Endocrinol
2022;14(3):267-274

8. Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J, Holl RW. Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. JAMA 2020;324:801-804.

9. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, Kwong RMW, Kumar P, Logan KM. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. Diabetes Care 2020;43:170-171. Epub 2020 Aug 17

10. Dżygało K, Nowaczyk J, Szwilling A, Kowalska A. Increased frequency of severe diabetic ketoacidosis at type 1 diabetes onset among children during COVID-19 pandemic lockdown: an observational cohort study. Pediatr Endocrinol Diabetes Metab 2020;26:167-175.

11. Alaqeel A, Aljuraibah F, Alsuhaibani M, Huneif M, Alsaheel A, Dubayee MA, Alsaedi A, Bakkar A, Alnahari A, Taha A, Alharbi K, Alanazi Y, Almadhi S, Khalifah RA. The Impact of COVID-19 Pandemic Lockdown on the Incidence of New-Onset Type 1 Diabetes and Ketoacidosis Among Saudi Children. Front Endocrinol (Lausanne) 2021;12:669302.

12. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A; Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Has covid-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care 2020;43:2870-2872. Epub 2020 Aug 10

13. Dilek SÖ, Gürbüz F, Turan İ, Celiloğlu C, Yüksel B. Changes in the presentation of newly diagnosed type 1 diabetes in children during the COVID-19 pandemic in a tertiary center in Southern Turkey. J Pediatr Endocrinol Metab 2021;22;34:1303-1309.

14. Vicinanza A, Messaaoui A, Tenoutasse S, Dorchy H. Diabetic ketoacidosis in children newly diagnosed with type 1 diabetes

mellitus: Role of demographic, clinical, and biochemical features along with genetic and immunological markers as risk factors. A 20-year experience in a tertiary Belgian center. Pediatr Diabetes 2019;20:584-593. Epub 2019 May 15

15. Szypowska A, Skórka A. The risk factors of ketoacidosis in children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2011;12:302-306. Epub 2010 Dec 5

16. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011;343:4092.

17. Tang JW, Bialasiewicz S, Dwyer DE, Dilcher M, Tellier R, Taylor J, Hua H, Jennings L, Kok J, Levy A, Smith D, Barr IG, Sullivan SG. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. J Med Virol 2021;93:4099-4101. Epub 2021 Apr 6

18. Sullivan SG, Carlson S, Cheng AC, Chilver MB, Dwyer DE, Irwin M, Kok J, Macartney K, MacLachlan J, Minney-Smith C, Smith D, Stocks N, Taylor J, Barr IG. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. Euro Surveill 2020;25:2001847.

19. Sepa A, Wahlberg J, Vaarala O, Frodi A, Ludvigsson J. Psychological stress may induce diabetes-related autoimmunity in infancy. Diabetes Care 2005;28:290-295.

20. Al-Zubeidi H, Leon-Chi L, Newfield RS. Low vitamin D level in pediatric patients with new onset type 1 diabetes is common, especially if in ketoacidosis. Pediatr Diabetes 2016;17:592-598. Epub 2015 Dec 23