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Increased Severity of Presentation Signs in Children with Newly Diagnosed Type 1 Diabetes during the COVID-19 Pandemic: A Tertiary Center Experience

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Keywords
Autoimmune diabetes · COVID-19 · Diabetes · Diabetes mellitus · Diabetic ketoacidosis · Seasonal variation

Abstract

Introduction: Diabetic ketoacidosis (DKA) is an important complication of type 1 diabetes mellitus (T1DM) which is worsened when the diagnosis of T1DM is delayed. The aim of this study was to evaluate the presentation patterns, severity, autoantibody status, and seasonal variability of newly diagnosed T1DM patients during the pandemic period of 2 years compared to those in the pre-pandemic period. ***Methods:*** In this single tertiary center retrospective cohort study, newly diagnosed T1DM patients were grouped as pre-pandemic and pandemic period. Age, gender, the month of diagnosis, hemoglobin A1c, venous blood gas parameters, duration of symptoms, glutamic-acid-decarboxylase-antibody (anti-GAD), islet-cell antibody (ICA), and insulin autoantibody levels were recorded. The data obtained were compared between the groups. ***Results:*** Number of patients presenting with DKA was significantly higher during the pandemic period (92 [65.7%] vs. 62 [40.8%] patients, $p < 0.001$). In terms of clinical severity of DKA, pH, and HCO3 levels were lower during the pandemic period ($p < 0.001$), while the number of patients presenting with severe DKA was significantly higher during the pandemic period (41 [44.6%] vs. 17 [27.4%] patients, $p = 0.031$). ICA positivity was significantly higher in patients admitted during the pandemic period (47 [36.4%] vs. 21 patients [16.9%], $p < 0.001$), especially in the second year of the pandemic ($p < 0.001$). Anti-GAD-ICA co-positivity was significantly higher in patients admitted during the pandemic period and also in second year of the pandemic ($p < 0.001$). ***Conclusion:*** DKA rates increased in newly diagnosed T1DM cases during the pandemic. Despite the relaxation of bans, the second year of the pandemic also saw increased rates of DKA and severe DKA compared to the pre-pandemic period. The significantly increased ICA positivity in the pandemic may support the effects of COVID-19 on autoimmune T1DM.

Introduction

The SARS-coronavirus-2 pandemic (COVID-19) has caused severe morbidity and mortality worldwide. On March 11, 2020, the World Health Organization declared a global pandemic, aiming to take measures to prevent the

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spread of the virus and ease the burden on the health system [1]. Delays in the diagnosis and treatment of non-COVID-19-related diseases such as cancer and cardiovascular diseases and difficulties in the follow-up of chronic diseases have emerged [2, 3].

When the diagnosis of type 1 diabetes mellitus (T1DM) is delayed, it can be complicated by diabetic ketoacidosis (DKA) [4]. DKA is a life-threatening condition, and even a single episode of ketoacidosis may affect brain development and cause low cognitive scores [5]. Since DKA is an important complication of T1DM, many studies have been conducted since the first months of the pandemic to investigate the DKA rates of patients with T1DM during the pandemic. Many of them have reported an increased admission rate with DKA [6–8]. In the following years, studies reporting high rates of DKA continued. In parallel, the effect of COVID-19 on the incidence of T1DM remains an intriguing research topic. It is noteworthy that different results were reported in studies evaluating T1DM incidence during the COVID-19 period. In addition to studies showing that the incidence has increased, studies showing that it has decreased have also been reported [9–11]. In studies reporting an increase in incidence, it has been argued that direct infection of pancreatic beta cells with the COVID-19 virus may increase the incidence of T1DM, while the decrease in incidence has been associated with decreased viral infections and less triggering of autoimmunity with the closure of schools and restriction of socialization [9]. Viruses can trigger autoimmunity and accelerate the progression from preclinical diabetes to clinically overt diabetes [12]. The diagnosis of T1DM may also show a seasonal distribution due to seasonal viral infections and subsequently induced autoimmunity. The aim of this study was to evaluate the presentation patterns, severity, T1DM autoantibody status, and seasonal variability of newly diagnosed T1DM patients during the pandemic period of 2 years compared to those in the pre-pandemic period and also T1DM cases admitted in the second year of the pandemic, when bans were largely lifted, were compared with those admitted in the first year.

Materials and Methods

After obtaining Local Ethics Committee approval (June 2022/389), the medical records of 422 patients who were treated in Pediatric Endocrinology unit of our tertiary health center between March 2018 and March 2022 were evaluated. In diagnosis of T1DM, the International Society for Pediatric and Adolescents Diabetes 2018 criteria were used [13]. Considering the possibility of neonatal DM, 3 patients who were younger than 6 months at the time of presentation, 6 patients diagnosed with MODY and DM associated with cystic fibrosis, metabolic disease, and steroid use, 26 patients diagnosed with type 2 DM with hyperglycemia accompanied by elevated insulin and c-peptide levels and insulin resistance findings such as acanthosis nigricans and started on insulin, 18-month-old patient with stress hyperglycemia after which insulin treatment was discontinued, and 94 patients with previously known T1DM presenting with DKA were excluded. Patients whose autoantibodies were found to be negative or who had not been tested for T1DM autoantibodies were also considered to have T1DM if they were clinically compatible, considering their presentation characteristics. In total, 292 (130 excluded) patients with newly diagnosed T1DM were included in the study.

Age at diagnosis and gender for demographic features, the month of diagnosis to assess seasonality, hemoglobin A1c level, venous blood gas (pH, bicarbonate [HCO3]) parameters to assess severity, time from onset of diabetes symptoms (polyuria and polydipsia) to presentation to assess delayed admission, glutamic-acid-decarboxylase-antibodies (anti-GAD), islet-cell antibodies (ICA), and insulin autoantibodies (IAA) levels in order to assess autoimmunity were recorded.

DKA was defined as a blood glucose level >200 mg/dL, pH <7.3 and/or HCO3 <15, and ketone positivity in urine. DKA patients were classified as mild ($7.2 \leq pH < 7.3$), moderate ($7.1 \leq pH < 7.2$), and severe ($pH < 7.1$ and/or $HCO3 < 5$) according to blood pH values. Patients were grouped as pre-pandemic (March 2018-March 2020) and pandemic period (March 2020-March 2022). Patients admitted during the pandemic period were also regrouped as first and second-year pandemic applicants. The data obtained were compared between the groups.

Statistical Analysis

The obtained data were evaluated using the IBM-SPSS (Version 20.0). All descriptive data of the study were analyzed by number, percentage, mean, median, standard deviation, and interquartile ranges. χ^2 tests were used to compare categorical data, and the Kruskall-Wallis test was used to compare continuous data. The seasonal variation was evaluated with the runs test. $p \leq 0.05$ was accepted for statistical significance.

Results

A total of 292 patients, 159 males (54.4%) and 133 females (45.6%), were included in the study. The median age at presentation was 10.4 years (IQR: 7.4–13.3). It was observed that 152 (52%) and 140 (48%) patients were diagnosed with T1DM before and during the pandemic, respectively. When the presentations of the patients at the time of diagnosis were evaluated, the number of patients presenting with DKA was significantly higher during the pandemic period (92 [65.7%] vs. 62 [40.8%] patients, $p < 0.001$). In terms of clinical severity of DKA, pH, and HCO3 levels were lower during the pandemic period ($p < 0.001$), while the number of patients presenting with severe DKA was significantly higher during the pandemic period

Table 1. Characteristics of newly diagnosed T1DM patients according to the time of diagnosis

	Pre-pandemic (n = 152)	Pandemic (n = 140)	p value
Sex			0.089
Male, n (%)	90 (59.2)	69 (49.3)	
Female, n (%)	62 (40.8)	71 (50.7)	
Age at diagnosis, years			0.263
Median (IQR 25–75)	10.51 (8.06–13.38)	10.04 (6.74–12.97)	
Age category, n (%)			0.356
6 month–5 years	24 (15.8)	31 (22.1)	
6 years–11 years	70 (46.1)	61 (43.6)	
12 years–18 years	58 (38.2)	48 (34.3)	
pH			<**0.001**
Median (IQR 25–75)	7.35 (7.21–7.39)	7.24 (7.08–7.34)	
HCO3			<**0.001**
Median (IQR 25–75)	19.55 (11.6–22.75)	11.35 (7.7–19.05)	
DKA at presentation (according to pH)			<**0.001**
DKA	62 (40.8)	92 (65.7)	
No DKA	90 (59.2)	48 (34.3)	
Severity of DKA			**0.031**
Severe DKA	17 (27.4)	41 (44.6)	
Mild-moderate DKA	45 (72.6)	51 (55.4)	
HbA1C			0.596
Median (IQR 25–75)	12.1 (10.8–14.2)	12.4 (10.95–14.15)	
Duration of symptoms (month)			**0.014**
Median (IQR 25–75)	0.5 (0.25–1)	0.78 (0.3–2)	
Month at diagnosis			0.356
Autumn	37 (24.3)	32 (22.9)	
Winter	41 (27.0)	34 (24.3)	
Spring	40 (26.3)	30 (21.4)	
Summer	34 (22.4)	44 (31.4)	
Anti-GAD			0.980
Negative	37 (29.6)	38 (29.5)	
Positive	88 (70.4)	91 (70.5)	
ICA			<**0.001**
Negative	103 (83.1)	82 (63.6)	
Positive	21 (16.9)	47 (36.4)	
IAA			0.343
Negative	4 (100)	4 (80)	
Positive	0 (0.0)	1 (20)	
Anti-GAD and ICA			**0.003**
Negative	133 (87.5)	103 (73.6)	
Positive	19 (12.5)	37 (26.4)	

HbA1C, hemoglobin A1c.

(41 [44.6%] vs. 17 [27.4%] patients, p = 0.031). ICA positivity among autoimmune markers was significantly higher in patients admitted during the pandemic period (47 [36.4%] vs. 21 patients [16.9%], $p < 0.001$) (Table 1).

Pandemic-era admissions (n = 140) were grouped as first (n = 79) and second-year (n = 61) admissions and compared with pre-pandemic admissions. Compared to the pre-pandemic period, the increase in the number of

Table 2. Characteristics of newly diagnosed T1DM patients according to the time of diagnosis

	Pandemic 1st year	Pandemic 2nd year	*p* (pandemic 1st year vs. 2nd year)	Pre-pandemic	*p1* (pre-pandemic vs. pandemic 1st year)	*p2* (pre-pandemic vs. pandemic 2nd year)	*p a* (among all groups)
Sex							
Male, *n* (%)	39 (49.4)	30 (49.2)	0.983	90 (59.2)	0.153	0.182	0.235
Female, *n* (%)	40 (50.6)	31 (50.8)		62 (40.8)			
Age at diagnosis, years							
Median (IQR 25–75)	9.8 (6.6–12.9)	10.3 (6.8–13.4)	0.977	10.5 (8.1–13.4)	0.422	0.619	0.528
Age category, *n* (%)							
6 month–5 years	18 (22.8)	13 (21.3)	0.977	24 (15.8)	0.422	0.619	0.733
6 years–11 years	34 (43.0)	27 (44.3)		70 (46.1)			
12 years–18 years	27 (34.2)	21 (34.4)		58 (38.2)			
pH							
Median (IQR 25–75)	7.2 (7.1–7.3)	7.2 (7–7.3)	1,000	7.4 (7.2–7.4)	<**0.001**	<**0.001**	<**0.001**
HCO3							
Median (IQR 25–75)	11.3 (8.3–19)	12.7 (6.5–20)	1,000	19.6 (11.6–22.8)	<**0.001**	<**0.001**	<**0.001**
DKA at presentation							
DKA, *n* (%)	53 (67.1)	39 (63.9)	0.697	62 (40.8)	<**0.001**	**0.002**	<**0.001**
No DKA, *n* (%)	26 (32.9)	22 (36.1)		90 (59.2)			
Severity of DKA, *n* (%)							
Severe DKA	21 (39.6)	20 (51.3)	0.266	17 (27.4)	0.165	**0.015**	0.051
Mild-moderate DKA	32 (60.4)	19 (48.7)		45 (72.6)			
HbA1C							
Median (IQR 25–75)	12.8 (11.5–14.2)	12.1 (10.4–14.1)	–	12.1 (10.8–14.2)	–	–	0.375
Duration of symptoms, months							
Median (IQR 25–75)	0.5 (0.3–1)	1 (0.5–2)	0.453	0.5 (0.3–1)	0.709	**0.013**	**0.017**
Season at diagnosis, *n* (%)							
Autumn	19 (24.1)	13 (21.3)	0.220	37 (24.3)	0.101	0.830	0.280
Winter	20 (25.3)	14 (23)		41 (27.0)			
Spring	12 (15.2)	18 (29.5)		40 (26.3)			
Summer	28 (35.4)	16 (26.2)		34 (22.4)			
Anti-GAD, *n* (%)							
Negative	20 (28.6)	18 (30.5)	0.771	37 (29.6)	0.880	0.854	0.971
Positive	50 (71.4)	41 (69.5)		88 (70.4)			
ICA, *n* (%)							
Negative	54 (77.1)	28 (47.5)	<**0.001**	103 (83.1)	0.313	<**0.001**	<**0.001**
Positive	16 (22.9)	31 (52.5)		21 (16.9)			
IAA, *n* (%)							
Negative	0 (0.0)	4 (80)	–	4 (100)	–	0.343	–
Positive	0 (0.0)	1 (20)		0 (0.0)			
Anti-GAD and ICA, *n* (%)							
Negative	65 (82.3)	38 (62.3)	**0.008**	133 (87.5)	0.282	<**0.001**	<**0.001**
Positive	14 (17.7)	23 (37.7)		19 (12.5)			

p, pandemic first year versus pandemic second year; *p1*, pre-pandemic versus pandemic first year; *p2*, pre-pandemic versus pandemic second year; *p a*, comparison among all the groups.

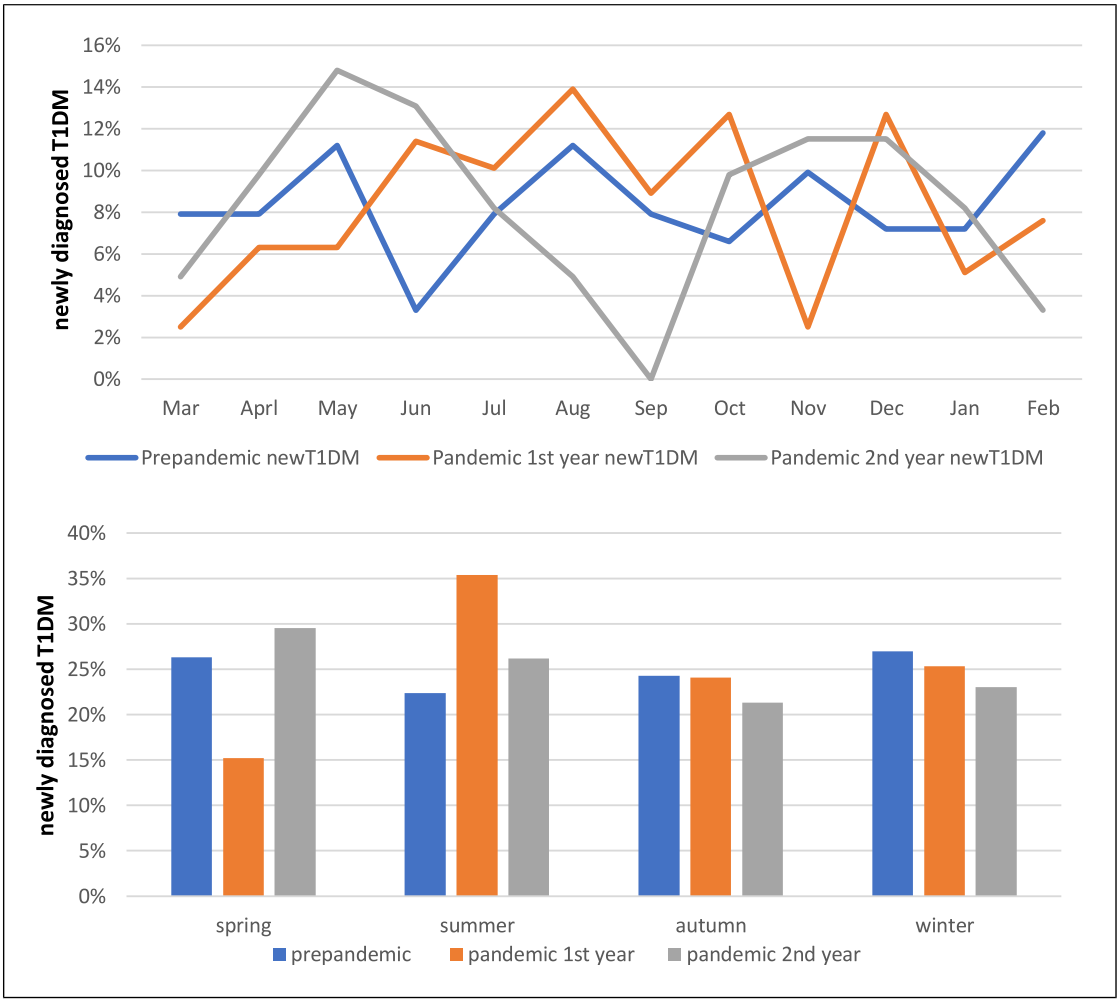

Fig. 1. Distribution graph of patients diagnosed with T1DM according to months (p: 0.667) and seasons (p: 0.280) between groups.

patients admitted with DKA was significant in both groups ($p < 0.001$), but the difference between admissions in the first and second year of the pandemic was not reflected in statistical significance ($p = 0.697$). When all groups were compared, the number of patients admitted with severe DKA was similar. Compared to the pre-pandemic period, the admission rates in the first year of the pandemic did not reach statistical significance (21 [39.6%] vs. 17 [27.4%], $p = 0.165$), while the admission rates in the second year were significantly higher (20 [51.3%] vs. 17 [27.4%], $p = 0.015$). There was no difference in severe DKA between first and second year of the pandemic. When evaluated in terms of the season of T1DM diagnosis, no significant difference was observed between the groups ($p = 0.280$). When autoantibody status was compared, ICA was significantly different between the groups ($p < 0.001$), this difference was more pronounced, especially in the second year of the pandemic, and Anti-GAD and IAA levels were similar. Anti-GAD-ICA co-positivity was significantly higher in second year of the pandemic ($p < 0.001$), also according to the first year of the pandemic ($p = 0.008$) (Table 2).

In the evaluation of the months in which T1DM was diagnosed before and after the pandemic, no significant relationship was observed between the groups (Fig. 1) ($p = 0.434$). In the seasonal evaluation, it was observed that T1DM was diagnosed more frequently during the pandemic, especially in the summer months (Fig. 1) ($p = 0.356$). When the relationship between the total number of COVID-19 cases in the country [14] and new T1DM diagnoses was evaluated, it was noticed that the number of patients diagnosed with T1DM was higher in the

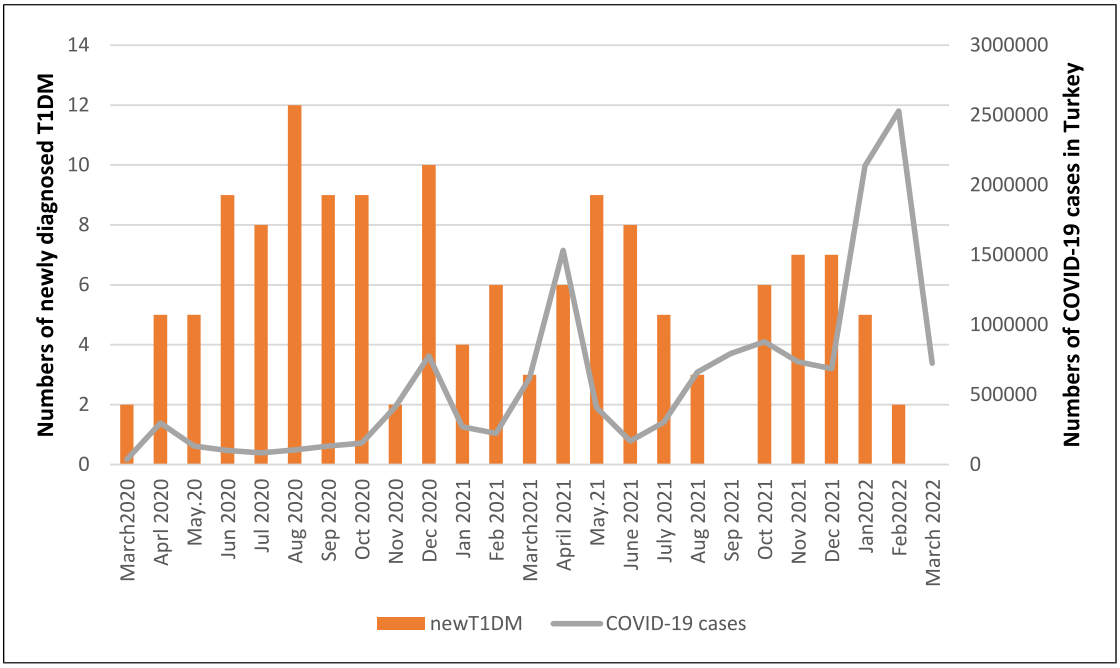

Fig. 2. Graphic representation of the monthly number of newly diagnosed T1DM patients according to the number of COVID-19 cases.

summer period when the number of COVID-19 cases decreased. The rates of newly diagnosed T1DM were lower in the winter period when the number of COVID-19 cases was higher (Fig. 2).

Discussion

During the pandemic, while emergency room visits decreased, an increasing number of admissions to hospitals due to DKA have been reported from different parts of the world [6, 7, 15–19]. The impact of the pandemic on the incidence and seasonal variability of T1DM continues to be investigated with different results from many regions [9, 10, 20–27]. In our study, in which the effect of the pandemic process on the diagnosis and presentation of T1DM was evaluated, it was observed that they presented with a more severe clinical picture during the pandemic. In the second year of the pandemic, DKA and severe DKA continued to occur, even though bans were relaxed, hospital services returned to the old routine and fears of COVID-19 were relatively reduced. In our study, diabetes autoantibody positivity was higher in the 2nd year. COVID-19 may have autoimmunologically affected the development of T1DM.

The sensitivity of patients or their families to evaluate the symptoms, recognize their seriousness, and apply to the emergency department was affected by both curfews and the instinct of families to protect themselves and their children during the pandemic period. Later recognition of symptoms leads patients to present with a more severe clinical picture to the hospital. We observed that patients with newly diagnosed T1DM presented with a higher rate and more severe DKA during the pandemic period compared to the pre-pandemic period. In a meta-analysis published by Alfayez et al. [28], similar to the findings in our study, they reported that the rate of presentation of newly diagnosed T1DM patients with DKA increased during the pandemic period, but there was no significant difference in the time until hospital admission. In the same article, it was emphasized that the reason for the increased rates of DKA might not only be a late presentation but that the awareness of families about diabetes symptoms may be variable [28]. In our study, the fact that the duration of symptoms was significantly longer in the pandemic supports that DKA is associated with late admission to the hospital. The rate of severe DKA was higher in the second year of the pandemic compared to the pre-pandemic period is consistent with symptom duration was significantly longer in the second year of the pandemic. In the multicenter study by Ponmani et al., it was argued that

delayed presentation alone was not explanatory in the development of DKA, as symptom durations were similar. In the study by Boboc et al., c-peptide levels were significantly lower in those who presented with DKA in the second year of the pandemic compared to those without DKA [27, 29]. In different studies independent of the pandemic, it has been emphasized that low insulin reserve is a factor in the development of DKA [30]. In our study, the high rates of DKA despite the relaxation of bans in the second year of the pandemic can be interpreted as low sensitivity of families to diabetes symptoms, or it can be considered as the prolonged effect of restrictions during the pandemic period.

The fact that newly diagnosed T1DM is generally detected at a higher rate in winter months compared to summer months is explained by increased viral infections in winter months [20, 31]. In studies conducted in Italy and the USA in the first months of the pandemic, it was reported that the number of newly diagnosed T1DM decreased, which may be explained by a decrease in the frequency of other viral infections due to restrictions during the pandemic period [9, 11]. Wolf et al. [11] reported a decrease in new diagnoses of T1DM in the first months of the pandemic, but more T1DM was diagnosed in the summer months. Similarly, Leiva-Gea et al. [23] and Kamrath et al. [22] reported an increase in T1DM cases in the summer months of the pandemic period, unlike the pre-pandemic period. In a large study conducted in Germany covering 2 years of pandemic and 8 years prior to the pandemic, new cases of T1DM were concentrated in the winter months before the pandemic, while they were concentrated in the summer season with the increasing incidence during the pandemic period [32]. Although our findings did not reach statistical significance, they support that more new T1DM diagnoses were made in the summer months compared to the pre-pandemic period. The relatively lower number of patients may have been insufficient to show the seasonal trend, and the population mobility in the summer months (especially in august) due to agricultural labor activities around our center may be effective in the seasonal trend relationship.

The TEDDY study [33] has shown that autoimmunity is triggered by respiratory infections, including coronavirus, especially in winter. The Centers for Disease Control and Prevention (CDC) [34] reports that a new diagnosis of DM after COVID-19 infection under the age of 18 is more likely than other acute respiratory infections. The demonstration of virus receptors on pancreatic beta cells in COVID-19 cell culture, animal, and organoid models has led to the hypothesis that COVID-19 may trigger the formation of T1DM by direct action [35–38]. However, another study has shown that these receptors are not present in pancreatic beta cells, and it has been evaluated that COVID-19 is unlikely to infect beta cells through direct receptors [39]. Ata et al. [40] evaluated COVID-19 antibodies in patients diagnosed with T1DM and reported no significant difference with the control group. McKeigue et al. [24] reported an increase in the incidence of T1DM and, contrary to what the CDC stated, there were less than 30 days between COVID-19 and the diagnosis of T1DM. The CDC study emphasized that the COVID-19 test, which is found to be positive when patients present to the hospital in relation to diabetes symptoms, may have been incorrectly associated with T1DM. Kayhan et al. [41] in a study conducted on adult patients who were found to be COVID-19 positive, they showed that autoantibody positivity persisted after 3 months in all patients who were initially found to be anti-GAD positive and in 50% of patients who were found to be ICA positive. Wang et al. found an increased rate of autoantibodies against immunomodulatory proteins in COVID-19 patients [42]. Boboc et al. also found that protein tyrosine phosphatase 2 antibodies (IA-2A) were significantly positive in newly diagnosed T1DM children with positive COVID-19 antibodies, and the combined positivity of three antibodies (anti-GAD+ICA+IA-2A) was significantly increased. In a study conducted in Africa, IA-2A and anti-GAD were found to be significantly positive during the pandemic period [25, 29]. Baechle et al. found an increase in the incidence of antibody positive T1DM in parallel with the increased incidence of T1DM in the pandemic. In the same study, it was found that there was no increase in the incidence of antibody negative T1DM, which would be expected to increase if direct beta-cell damage was responsible for the pathogenesis of the increase in T1DM incidence [32]. In their in vitro study, Heide et al. [43] pointed out that the pancreatic beta cell can be infected by COVID-19 but that many factors must coexist for this to occur and that pancreatic microvascular damage through microvascular thrombosis may increase the incidence of T1DM in predisposed individuals. COVID-19 infection may also cause autoimmune beta-cell damage by causing epigenetic changes [44]. All these studies support that COVID-19 can trigger autoimmunity against pancreatic beta cells. Similar to these studies, in our study, ICA was found to be significantly more positive in the pediatric population compared to the pre-pandemic period. When the first and second years of the pandemic were evaluated separately, it was observed that ICA positivity increased significantly in the second year compared to the pre-pandemic and first year. Considering that the majority of

the population was infected with COVID-19 in the second year of the pandemic, with the decrease in the bans and the first year behind, the fact that ICA positivity was found to be significantly higher in the second year of the pandemic suggested that COVID-19 may be effective in the development of T1DM by autoimmunity.

It has been reported that T1DM may be triggered by psychological stressors and may present with symptoms [45, 46]. Multiple antibody positivity increases the risk of developing T1DM compared to single antibody positivity [47]. In studies conducted in our country, GAD was found to be significantly positive during the pandemic period [18, 48]. In Finland, which has the highest incidence of T1DM, anti-GAD was found to be significantly positive during the pandemic period. Again, multiple antibody positivity were found to be significant, but since the positivity rate of COVID-19 antibody and the incidence increase rate were not compatible, it was emphasized that the indirect effects of COVID-19 may play a role in the increase in incidence [26]. While multiple antibody positivity is associated with a higher risk of developing overt T1DM, the duration of progression to overt T1DM in antibody-positive individuals varies. Anti-GAD positivity has been associated with slow progression [49, 50]. Combined positivity of anti-GAD-ICA and ICA in our cohort is significantly higher in pandemic period. In addition, ICA and anti-GAD-ICA positivity in the second year of the pandemic was significantly higher compared to the pre-pandemic period and the first year of the pandemic. Considering that the majority of the population was infected with COVID-19 in the second year of the pandemic, the autoimmune effect of COVID-19 may have been more pronounced in the second year of the pandemic. There is an asymptomatic latent period until autoimmune T1DM becomes clinically evident. The more pronounced ICA and anti-GAD-ICA positivity in the second year of the pandemic may also be related to the acceleration of the autoimmune asymptomatic phase by COVID-19.

The fact that it was a single-center retrospective study can be considered as a limitation of our study; our center accepts patients from a wide geography due to the low number of pediatric endocrinology clinics in its region. For this reason, it would be useful to consider that even though it is a single-center study, it can evaluate a wide geography which is hinterland of middle black sea region. According to the 2022 data of the Turkish Statistical Institute, the population in this region is 4,189,443. Our limitations also include the fact that other T1DM autoantibodies (Zinc transporter 8 antibody [ZnT8], IAA and protein tyrosine phosphatase 2 antibody [IA-2A]) were not routinely studied in our center and data about IAA status is unknown in almost all patients. The patients' COVID-19 infection history and antibody levels were not known.

In conclusion, in this study, we found that DKA rates increased in newly diagnosed T1DM cases during the pandemic period. Despite the relaxation of bans, the second year of the pandemic also saw increased rates of DKA and severe DKA compared to the pre-pandemic period. As the incidence of T1DM has increased over the years, further studies will clarify whether COVID-19 contributes to this increase through direct beta-cell infection or by triggering autoimmunity or whether it causes a temporary increase in incidence by accelerating the clinical manifestation of T1DM, as in other viral infections. It would be appropriate to increase awareness of the first clinical symptoms of T1DM to prevent presentations with severe DKA.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Ondokuz Mayıs University, Faculty of Medicine (June 2022/389). The study was conducted in accordance with the Helsinki Declaration. Our retrospective chart review study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University with the decision number OMÜ KAEK 2022/287. Informed consent was waived by the Ondokuz Mayıs University Faculty of Medicine Clinical Research Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Elif İzci Güllü, Leyla Akın, and Murat Aydın contributed to the study conception and design. Material preparation and data collection were performed by Elif İzci Güllü. Statistical analysis was performed by Mehmet Enes Gökler. The first draft of the manuscript was written by Elif İzci Güllü and all authors commented on previous versions of the manuscript and critically reviewed the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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