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ORIGINAL ARTICLE

Evaluation of the Presentation of Newly Diagnosed Type 1 Diabetes Mellitus in Children During and After the COVID-19 Pandemic

Türkiye'nin Güneyindeki İkinci Basamak Bir Sağlık Merkezinde, COVİD-19 Salgını Sırasında ve Sonrasında Tip 1 Diyabet Tanısı Alan Çocukların Tanı Özelliklerinin Değerlendirilmesi

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ABSTRACT

Background: The COVID-19 pandemic has been a global health problem with high morbidity and mortality. In this study, it was aimed to compare the clinical and laboratory findings of patients diagnosed with type 1 diabetes mellitus (T1D) during the pandemic and after the pandemic.
Method: This is a 30-month-single-center, cross-sectional study. The time between October 2020 and December 2021 was defined as the pandemic period, and between January 2022 and March 2023 as the post-pandemic period. During these periods, clinical and laboratory parameters of pediatric patients diagnosed with T1D were compared at the time of admission.
Results: While 87 patients were diagnosed during the pandemic period, 86 patients were diagnosed during the post-pandemic period. The rate of male patients diagnosed during the pandemic period was significantly higher (56%, 36%, respectively, p=0.007). Anti-islet Cell antibody (ICA) positivity was statistically significantly higher in those diagnosed during the pandemic period. (52.6%, 18.6%, respectively, p<0.001). There was no difference between the groups in terms of hemoglobin A1C, thyroid autoantibodies and tissue transglutaminase antibodies (p>0.05). C peptide levels were significantly lower in those diagnosed during the pandemic period (0.39±0.4, 0.63±0.6, respectively, p=0.021). Admissions with severe acidosis were more common during the pandemic than those admitted after the pandemic (29.9%, 16.3%, respectively, p=0.151).
Conclusion: The numbers of children with T1D newly diagnosed in a secondary health center were similar during and after the pandemic. In the pandemic period, admissions with autoantibody positivity, low C-peptide and severe acidosis were more common.

Keywords: COVID 19, diabetes mellitus type 1, newly diagnosed

ÖZ

Amaç: COVİD-19 salgını yüksek morbidite ve mortaliteye sahip küresel bir sağlık sorunu olmuştur. Bu çalışmada pandemi sırasında ve pandemi sonrasında tip 1 diyabet (T1D) tanısı alan hastaların klinik ve laboratuvar bulgularının karşılaştırılması amaçlandı.
Yöntem: 30 aylık, tek merkezli, kesitsel bir çalışma şeklinde dizayne edilen bu çalışmada Ekim 2020 ile Aralık 2021 arası pandemi dönemi, Ocak 2022 ile Mart 2023 arası ise pandemi sonrası dönem olarak tanımlandı. Bu iki dönemde başvuran yeni tanı alan T1DM hastalarının klinik ve laboratuvar parametreleri karşılaştırıldı.
Bulgular: Pandemi döneminde 87 hastaya tanı konulurken, pandemi sonrası dönemde 86 hastaya tanı konuldu. Pandemi döneminde tanı alan erkek hasta oranı anlamlı olarak daha yüksekti (sırasıyla %56, %36, p=0,007). Pandemi döneminde tanı konulanlarda Anti-Adacık Hücre Antikoru (ICA) pozitifliği istatistiksel olarak anlamlı derecede yüksekti. (sırasıyla %52,6, %18,6, p<0,001). Gruplar arasında hemoglobin A1C, tiroid otoantikorları ve doku transglutaminaz antikorları açısından fark yoktu (p>0,05). Pandemi döneminde tanı konulanlarda C peptid düzeyleri anlamlı derecede düşüktü (sırasıyla 0,39±0,4, 0,63±0,6, p) =0,021). Pandemi sırasında şiddetli asidoz nedeniyle başvurular, pandemi sonrasına göre daha sık görüldü (sırasıyla %29,9, %16,3, p=0,151).
Sonuç: İkinci basamak sağlık merkezimizde yeni tnaı koyulan T1D hastası çocukların sayısı pandemi sırasında ve sonrasında benzerdi. Pandemi döneminde otoantikor pozitifliği, C-peptid düşüklüğü ve ciddi asidoz şikayetleriyle başvurular daha sıktı.

Anahtar Kelimeler: covid 19, diabetes mellitus type 1, yeni tanı

Introduction

The World Health Organization declared COVID-19 a pandemic on March 24, 2020, as it caused high morbidity and mortality in a short time and turned into a global health problem (1). The first case was seen in Türkiye on March 11, 2020 (2). COVID-19 disease can affect the health of children directly or indirectly, and this situation can cause many social, biological and economic negativities. Many studies have revealed interesting findings related to the increase in the prevalence of newly diagnosed type 1 diabetes during the pandemic period and the effect of COVID-19 on the clinical severity of the symptoms at the time of first admission (3,4). During the pandemic period, some studies showed that there was a significant decrease in vitamin D levels in children and it was associated with decreased sun exposure during confinement (5). In this study, the clinical and laboratory characteristics of the newly diagnosed type 1 diabetes mellitus (T1D) patients during and after the pandemic were compared at the time of diagnosis.

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Material and Methods

This descriptive cross-sectional study was approved by the Gaziantep University Faculty of Medicine Clinical Research Ethics Committee (Number:01/2023). All patients younger than 18 years of age who were diagnosed with T1D at Gaziantep Gynecology and Children's Hospital between October 2020 and March 2023 were included in the study. We diagnosed patients with type 1 diabetes according to the International Society for Pediatric and Adolescent Diabetes 2018 criteria (6). All diabetic ketoacidosis (DKA) and non-DKA (non-DKA) patients (venous pH>7.3 or bicarbonate >15 mmol) diagnosed as T1D with plasma glucose >200 mg/dl and ketonemia or ketonuria were included in this study. DKA was classified as plasma glucose >200 mg/dl, presence of ketonemia or ketonuria, venous pH <7.3 or bicarbonate <15 mmol/L (mild DKA); pH<7.2 or bicarbonate <10 mmol/L (moderate DKA); pH<7.1 or bicarbonate <5 mmol/L (severe DKA). At the time of diagnosis, HbA1C (%), C-peptide, islet cell antibody (ICA), glutamic acid decarboxylase antibody (GAD), anti-insulin antibody (Anti IA), anti-thyroid peroxidase antibody (Anti TPO) and celiac antibodies (tissue transglutaminase IGA, IGG) were evaluated. At the time of the study, the same micro enzyme-linked immunosorbent assay (ELISA) was used to measure autoantibody positivity. We also evaluated the 25(OH) D3, Vitamin B12 and anti-HBS levels of the patients.

According to the data of the Turkish Statistical Institute (TUİK) dated 31 December 2021, the population of Türkiye was 84 million 580 thousand 273 people (7). As of January 2022, covid 19 vaccine (Sinovac or BioNTech) has been applied for 1 year in Türkiye, and approximately 138 million doses of vaccine have been applied to individuals over the age of 18 years (8). For this reason, the period between October 2020 and December 2021 was defined as the pandemic period, and the period between January 2022 and March 2023 was defined as the post-pandemic period. Based on these data, we divided the patients into two groups as those diagnosed during and after the pandemic.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and min-max where appropriate). Chi-square test was used to compare categorical expressions. Shapiro-Wilk test was employed to determine whether the parameters in the study showed normal distribution. Mann Whitney U test was used for the parameters that did not show normal distribution. Statistical significance level was taken as 0.05 in all tests.

Results

Of the 173 patients included in the study, 80 (46.2%) were male and 93 (53.9%) were female. Their mean age was 15.7 (±3.8) years. Only 38 patients (22%) were refugees. 57 patients (32.9%) were in pubertal period. Anti-HBs was positive in only 69 patients (39.9%). The numbers of Anti-HBs positive patients were similar in the groups (p=0.59). The mean level of 156 patients whose vitamin D levels were checked was 14.1±7.8 ng/ml. Of the patients, 130 (83.3%) whose vitamin D values were checked had a vitamin D level below 20 ng/ml and had vitamin deficiency. Vitamin D value was higher in male patients than in female patients (p=0.029). Also, Vitamin D levels of pandemic and post-pandemic patients were similar (p=0.59).

Of the patients, 87 (50.3%) were diagnosed during the pandemic period (group 1), and 86 (49.7%) were diagnosed during the post-pandemic period (group 2). The presence of anti-ICA was found higher in group 1 (p<0.001). The co-positivity of Anti GAD and ICA antibodies was higher in group 1 (39/87 [%44.8] and 16/86 [%18.6], respectively) (p<0.001). Again, in group 1, the positivity of 3 antibodies together (Anti-Gad, ICA and Anti insulin) was statistically higher (7/87 [%8], 2/86 [%2.3], respectively) (p=0.001). There was no difference between the groups in terms of hemoglobin A1c, thyroid autoantibodies and tissue transglutaminase antibodies (p>0.05). Potassium and C-peptide values were higher in group 2 compared to group 1 (p=0.037; p=0.021, respectively); Vitamin B12 value was observed low (p=0.011). The low potassium in group 1 was considered due to the high number of patients presenting with DKA. The comparison of other values between the groups is shown in Table 1.

When male and female patients were compared, the presence of Anti-GAD was higher in female patients than in male patients (p=0.046). No significant finding was found between the other parameters in Table 2 and the groups (p>0.05). Height SD and HbA1c values of Turkish patients were higher than those of refugee patients (p=0.020).

The number of people diagnosed with non-DKA was higher in the post-pandemic period than in the pandemic period, but it was not statistically significant (47 [54.7%], 37 [42.5%], respectively) (p=0.15). Similarly, the number of admissions with severe acidosis was higher during the pandemic period than in the post-pandemic period. (respectively 26 [29.9%], 14 [16.3%]) (p=0.15). Among the patients diagnosed during the pandemic period, 49(56.3%) male patients were significantly more than female patients (p=0.007).

While patients in the pandemic period were most diagnosed in November (19 cases) and March (11 cases), the most diagnosed months were January (12 cases) and October (9 cases) in the post-pandemic period. While 11 patients were diagnosed during the pandemic period in the summer season, only 4 patients were diagnosed during the post-pandemic period.

In terms of HbA1c levels, there was no significant difference between the pandemic and post-pandemic periods. During the pandemic period, SARS-CoV-2 PCR test was performed and only 2 patients were positive with resistant severe acidosis and respiratory distress and significantly higher infection indicators.

Table 1 Evaluation of laboratory and clinical characteristics of 2 groups

Related parameters	Group 1 (n=87)	Group 2 (n=86)	p†
	n(%)	n(%)	
Sex			
Male	49 (56.3)	31 (36)	0.007**
Female	38 (43.7)	55 (64)	
Puberty	27 (31)	30 (34.9)	0.590
Nationality			
Immigrant	21 (24,1)	17 (19.8)	0.488
Turkish	66 (75.9)	69 (80.2)	
DM in the family	7 (8)	5 (5.8)	0.563
Anti GAD	50 (64.1)	50 (58.1)	0.434
Anti ICA	41 (52.6)	16 (18.6)	<0.001**
Anti insulin	6 (7.7)	3 (3.5)	0.238
Celiac antibody	10 (11.5)	9 (10.5)	0.829
Anti TPO	18 (20.7)	16 (18.6)	0.730
Anti HBs	33 (37.9)	36 (41.9)	0.598
Acidosis severity			
none	37 (42.5)	47 (54.7)	0.151
1	13 (14.9)	16 (18.6)	
2	11 (12.6)	9 (10.5)	
3	26 (29.9)	14 (16.3)	
	Mean ± SD	Mean ± SD	p‡
Age (years)	12.,2±3.8	9.75±3.81	0.519
Height (cm)	138.2±22.6	134.1±23.4	0.181
Height SD	0.023±1.1	-0.11±1.2	0.415
Weight (kg)	35.6±15.9	33.9±19.4	0.199
Weight SD	-0.16±1.2	-0.45±1.1	0.075
Laboratory values (at diagnosis) Glucose (mg/dl)	456.5±106.9	478.4±15.0	0.685
Sodium (mmol/L)	133.2±3,8	145.1±107.3	0.447
Potassium (mmol/L)	3.60±0.5	3.74±0.4	0.037*
C peptide (ng/ml)	0.39±0,4	0.63±0.6	0.021*
HbA1c (%)	12.9±1.6	12.5±2.0	0.265
Insulin (µIU/mL)	2.91±2.8	3.58±2.9	0.079
Vitamin D (ng/ml)	13.7±7.1	14.5±8.4	0.598
Vitamin B12 (pg/ml)	465.4±224.1	386.9±188.1	0.011*
			-

** p<0,05, **p<0,001, †: chi-square, ‡: Mann Whitney U*

GAD: Glutamic acid decarboxylase, ICA: islet cell antibody, TPO: thyroid peroxidase

Table 2 Laboratory and clinical characteristics of the patients by gender

Related parameters	Male (n=80)	Female (n=93)	p†
	n(%)	n(%)	
Puberty	27 (33.8)	30 (32.3)	0.835
Nationality			
Immigrant	18 (22.5)	20 (21.5)	0.875
Turkish	62 (77.5)	73 (78.5)	
DM in the family	6 (7.5)	6 (6.5)	0.787
Anti GAD	40 (53.3)	60 (67.4)	0.046*
Anti ICA	29 (38.7)	28 (31.5)	0.334
Anti insulin	6 (8)	3 (3.4)	0.195
Celiac antibody	5 (6.3)	14 (15.1)	0.065
Anti TPO	14 (17.5)	20 (21.5)	0.509
Anti HBs	36 (45)	33 (35.5)	0.202
Acidosis severity			
none	40 (50)	44 (47.3)	0.417
1	13 (16.3)	16 (17.2)	
2	12 (15)	8 (8.6)	
3	15 (18.8)	25 (26.9)	
	Mean ± SD	**Mean ± SD**	p‡
Age (years)	10.40±3.90	9.40±3.65	0.151
Height (cm)	140.2±21.3	132.7±24.0	0.097
Height SD	0.05±1.1	-0.13±1.1	0.313
Weight (kg)	36.6±16.7	33.2±18.5	0.100
Weight SD	-0.19±1.2	-0.41±1.2	0.255
Laboratory values (at diagnosis) Glucose (mg/dl)	478.8±131.3	457.6±30.2	0.364
Sodium (mmol/L)	145.3±111.4	133.8±3.8	0.208
Potassium (mmol/L)	3.67±0.5	3.68±0.4	0.890
C-peptide (ng/ml)	0.45±0.4	0.58±0.6	0.534
HbA1c (%)	12.4±1.9	12.9±1.7	0.105
Insulin (µIU/mL)	2.88±2.5	3.57±3.2	0.231
Vitamin D (ng/ml)	15.2±7.1	13.2±8.3	0.029*
Vitamin B12 (pg/ml)	441.6±205.3	409.9±212.5	0.234

** p<0,05, **p<0,001, †: chi-square, ‡: Mann Whitney U*

GAD: Glutamic acid decarboxylase, ICA: islet cell antibody, TPO: thyroid peroxidase

Discussion

In this study, the clinical and laboratory characteristics of newly diagnosed patients were evaluated during and after the COVID-19 epidemic for a total of 30 months. Similar to the publications reported from our country, no difference was found in the frequency of patients diagnosed between the two periods (9). However, it has been shown that applications with severe diabetic ketoacidosis are more common during the pandemic period. Additionally, in our study, we found significantly higher antibody positivity and low C-peptide levels in patients diagnosed during the pandemic period.

Although its etiology is not clear, type 1 diabetes mellitus is a multifactorial disease. Especially in individuals with genetic predisposition, exposure to infectious agents (especially viruses) at an early age is affected by environmental factors such as toxins, food, chemicals, as well as triggering factors such as psychosocial stress (10,11).

The relationship between SARS-CoV-2 infection and incipient T1D development is unclear. A population-based study conducted in Germany between January 2020 and June 2021 among individuals younger than 18 years old showed that the observed incidence was significantly higher than the expected incidence of the new type of T1D (12). However, this study did not provide evidence to prove that the COVID-19 pandemic has had a direct impact on this increased incidence. In a study of 92 centers worldwide, no increase in pediatric new-onset T1DM was observed during the COVID-19 pandemic (13). In our study, the prevalence of newly diagnosed T1D patients during the active pandemic and post-pandemic periods was similar. Our results are in line with two large cohort studies that found no evidence of a direct link between SARS-CoV-2 infection and incipient T1D development (14,15)

A recent international multicenter study based on data from 13 national diabetes registries reported a higher prevalence of diabetic ketoacidosis (DKA)

at diagnosis of T1D among people younger than 18 years of age than the estimated prevalence in 2020 and 2021. However, the observed prevalence was not significant in all countries included in this study (16). In our study, although the number of patients with severe DKA was moderately high in the pandemic period, there was no statistically significant difference.

SARS-CoV-2 causes effects not only in the lungs but also in many organs in the body, including endocrine organs. Viral tropism in these tissues is mediated by receptors for the coronavirus spike protein such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). It is known that SARS-CoV-2 can multiply by infecting the cells of the exocrine pancreas and pancreatic islets through these pathways (17).

Many studies have shown that COVID-19 is a risk factor for autoimmune disease (18,19). The studies by Chang et al. (20) and Tesch et al. (21) have comprehensively demonstrated the existence of various new-onset autoimmune conditions (rheumatoid arthritis, systemic lupus erythematosus, celiac disease, etc.) after COVID-19. Again, in some studies, the relationship between endocrine autoimmune diseases such as thyrotoxicosis and hashimoto thyroiditis and COVID-19 was discussed (22,23). Although there are different debates on the relationship between diabetes autoimmunity and Covid 19, Schiaffini et al. (24) reported in their study that COVID-19 infection would not cause diabetes autoimmunity even if it had an effect on the T1D clinic. During the echovirus 16 epidemic in Cuba, an increase in the co-occurrence of ICA and anti-GAD positivity was observed in children (25). It has been shown that having more than one antibody positivity increases the risk of developing type 1 diabetes compared to a single diabetes autoantibody positivity (26,27). In our study, ICA antibody positivity and other diabetes antibodies co-existent were found significantly higher in patients diagnosed during the pandemic period.

In another study, Sepa et al. (28) reported a high anti-GAD positivity among children participating in their study, and also noted that exposure to psychosocial stressors in children, with or without a family history of diabetes, may be considered as a risk factor for autoimmune type 1 diabetes. Accordingly, it can be thought that the reason for the high antibody positivity in patients diagnosed during the pandemic period in our study can be attributed to the psychosocial stress created by the pandemic.

It has been reported that the new diagnosis season of patients in Türkiye is mainly in winter and autumn months (29). However, in our study, there was no decrease in the number of patients diagnosed during the summer season, especially during the pandemic, and 11 patients were diagnosed with T1D, while the number of patients after the pandemic was only 4 patients. We thought that this may be due to the fact that the pandemic period Covid 19 infections continued in the summer period.

C-peptide, a molecule produced in insulin equimolar concentration, has become an established biomarker of insulin secretion in diabetic patients. Measurement of the C-peptide level can be helpful in clinical practice, particularly in patients currently scheduled to receive exogenous insulin therapy, to assess the residual function of insulin-producing β-cells (30). Significantly lower C-peptide levels in the pandemic-era patients suggested that the beta-cell reserve in the pancreas was more severely affected.

Various mechanisms by which vitamin D is effective in regulating immune response support, the role of vitamin D in the pathogenesis of autoimmune diabetes, and vitamin D as a protective compound for diabetes have been suggested. The epidemiological evidence and observational studies suggesting that adequate vitamin D is associated with a reduced risk of developing type 1 diabetes further support this concept (31). We evaluated 25(OH)vitamin D levels in 156/173 (90.1%) of our patients. Severe vitamin D deficiency (<20 ng/ml) was present in 83.3% (130/156) of our patients whose vitamin D levels were checked without any difference between pandemic or post-pandemic periods. This situation underlines the need to evaluate Vitamin D levels in children with T1D diagnosed.

Type 1 diabetes (T1DM) is predicted to result in impaired immunological response to vaccines. HBV vaccine is routinely administered to every newborn child according to the national vaccination schedule. Although there are different data regarding the humoral immune response to hepatitis B vaccine in patients with type 1 diabetes, only 39% of all our newly diagnosed patients had an adequate Anti-HBs response (32).

It has been stated that SARS-CoV-2 may cause an increase in aldosterone secretion and a decrease in angiotensin II by decreasing ACE2 expression, which may lead to an increase in renal potassium loss (33). The significant low potassium in patients diagnosed during the pandemic may be explained by a COVID-19 infection that was experienced without being symptomatic. Unfortunately, we did not routinely evaluate our patients for the presence of COVID-19 infection.

Studies evaluating vitamin B12 deficiency are mostly related to type 2 diabetes mellitus and metformin treatment (34). There is no definitive information on the relationship between T1D and B12 deficiency. In our study, although there was a significant difference in vitamin B12 levels between the two groups, there was no deficiency in either group.

In conclusion, our study, in which we detected serious vitamin D deficiency in all groups, revealed the need to evaluate vitamin D, especially in extraordinary periods such as pandemics, when sunlight exposure is highly restricted. Moreover, we found significantly high antibody positivity and low levels of C-peptide in patients diagnosed during the pandemic period. Again, although it was not statistically significant, the

presence of severe acidosis was higher at the time of diagnosis during the pandemic period. In order to clearly demonstrate the relationship between Covid 19 and T1D, larger series of reports are needed.

Limitations of the study

Covid 19 PCR test was not performed on the patients who did not have any signs.

As it was a single center study, we could not include all newly diagnosed T1D children in Gaziantep in our study. However, since our hospital is a state hospital, it is a hospital that is easily accessible and preferred by the public, and it also accepts patients from neighboring provinces when necessary. Therefore, our findings may represent Southern Türkiye with different ethnicities and cosmopolitan population structure.

Declarations

Funding and/or Conflicts of interests

The authors declare that they have no conflict of interest

Data availability

Data are available from the corresponding author upon reasonable request.

Ethical Statement

Approval for the study was received from Gaziantep University Faculty of Medicine ethics committee unit.

Author Contributions

Concept- Fatma Özgüç Çömlek, Design- Fatma Özgüç Çömlek Supervision- Fatma Özgüç Çömlek Materials, Fatma Özgüç Çömlek, data Collection and /or Processing- Fatma Özgüç Çömlek, Semine Özdemir Dilek, Analysis and /or interpretation- Fatma Özgüç Çömlek Literature Review Fatma Özgüç Çömlek; Writer- Fatma Özgüç Çömlek ;Critical Review- Fatma Özgüç Çömlek, Semine Özdemir Dilek

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