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Original Article

Impact of SARS-CoV-2 Infection on Diabetic Ketoacidosis in Children with Newly Diagnosed Type-1 Diabetes: A Prospective Multicenter Study

Yeni Tanı Konmuş Tip 1 Diyabetli Çocuklarda SARS-Cov-2 Enfeksiyonunun Diyabetik Ketoasidoz Üzerindeki Etkisi: Prospektif Çok Merkezli Bir Çalışma

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ABSTRACT

Objective: The coronavirus disease pandemic has raised concerns about a possible link between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and both the development of type 1 diabetes (T1D) and increased rates and severity of diabetic ketoacidosis (DKA) at diagnosis. However, existing evidence is largely retrospective and inconclusive. This prospective multicenter study aimed to evaluate the association between SARS-CoV-2 infection and the rate and severity of DKA in children newly diagnosed with T1D and to assess the prevalence of SARS-CoV-2 exposure in this population.

Methods: This study included 133 pediatric patients newly diagnosed with T1D across three tertiary centers in Türkiye between April 2021 and April 2022. SARS-CoV-2 status was determined at diagnosis using polymerase chain reaction and serological tests (IgM, IgG); IgG testing was repeated after 21 days. Patients were categorized into three groups: active infection, past infection, and no infection. The prevalence of SARS-CoV-2 exposure was also analyzed.

Results: SARS-CoV-2 seropositivity was found in 39% of patients. DKA was present in 76.9% of those with active infection, 66.6% of those with past infection, and 54.3% of those without infection. Although DKA was more frequent in those with SARS-CoV-2 exposure, the difference was not statistically significant (p=0.240). DKA severity also showed no significant variation among groups (p=0.162).

Conclusions: DKA was the predominant presentation regardless of SARS-CoV-2 status, with no significant difference in frequency or severity. These findings suggest that increased DKA rates may be more

ÖZ

Amaç: Koronavirüs hastalığı pandemisi, Şiddetli Akut Solunum Yolu Sendromu Koronavirüs 2 (SARS-CoV-2) enfeksiyonunun tip 1 diyabetin (T1D) gelişimi ile ilişkili olabileceği ve tanı anında diyabetik ketoasidozun (DKA) sıklığı ve şiddetinde artışa neden olabileceği yönünde endişelere yol açmıştır. Ancak mevcut kanıtlar büyük ölçüde retrospektif olup kesin değildir. Bu çok merkezli prospektif çalışma, SARS-CoV-2 enfeksiyonu ile yeni tanı almış T1D'li çocuklarda DKA sıklığı ve şiddeti arasındaki ilişkiyi değerlendirmeyi ve bu grupta SARS-CoV-2 maruziyetinin yaygınlığını belirlemeyi amaçlamıştır.

Yöntemler: Çalışmaya, Nisan 2021 ile Nisan 2022 arasında Türkiye'de üç üçüncü basamak sağlık merkezinde yeni T1D tanısı alan 133 çocuk hasta dahil edildi. SARS-CoV-2 durumu, tanı anında polimeraz zincir reaksiyonu ve serolojik testler (immünoglobulin (Ig)M, IgG) ile, 21 gün sonra ise sadece IgG testiyle değerlendirildi. Hastalar aktif enfeksiyon, geçirilmiş enfeksiyon ve enfeksiyon belirtisi olmayanlar olarak üç gruba ayrıldı. SARS-CoV-2 maruziyetinin genel yaygınlığı da analiz edildi.

Bulgular: Hastaların %39'unda SARS-CoV-2 seropozitifliği saptandı. DKA, aktif enfeksiyonu olanların %76,9'unda, geçirilmiş enfeksiyonu olanların %66,6'sında ve enfeksiyon belirtisi olmayanların %53'ünde görüldü. SARS-CoV-2 maruziyeti olanlarda DKA oranı daha yüksek olsa da bu fark istatistiksel olarak anlamlı değildi (p=0,240). DKA şiddeti açısından da gruplar arasında anlamlı fark yoktu (p=0,162).

Sonuçlar: DKA, tüm gruplarda en yaygın başvuru şekliydi ve SARS-CoV-2 enfeksiyon durumu ile sıklık ya da şiddet açısından anlamlı bir fark gözlenmedi. Bu bulgular, yüksek DKA oranlarının doğrudan

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related to healthcare access issues during the pandemic than to direct viral effects.

Keywords: SARS-CoV-2, type 1 diabetes, diabetic ketoacidosis, children, COVID-19

viral etkilerden çok pandemiye bağlı sağlık hizmetlerine erişim kısıtlılıklarıyla ilişkili olabileceğini düşündürmektedir.

Anahtar kelimeler: SARS-CoV-2, tip 1 diyabet, diyabetik ketoasidoz, çocuk, COVID-19

INTRODUCTION

The coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a significant and persistent impact on overall health worldwide. Through June 8, 2025, there have been more than 778 million reported cases and 7 million reported deaths[1]. Apart from causing acute respiratory disease, COVID-19 has also been linked to a myriad of chronic sequelae collectively known as 'long COVID' that encompass neuropsychiatric, cardiovascular, gastrointestinal, and endocrine manifestations[2]. Among the endocrine effects, there has been growing interest in a potential link between SARS-CoV-2 and type 1 diabetes (T1D)[3,4].

T1D accounts for 5-10% of all diabetes cases and represents the vast majority of childhood-onset diabetes[5]. Similar to certain viruses, such as Coxsackievirus B, enterovirus, and rubella, SARS-CoV-2 has been hypothesized to either directly infect pancreatic tissue or trigger autoimmune mechanisms leading to β-cell destruction, though the exact mechanism remains unclear[6-8]. These theoretical concerns gained further traction as several early observational studies reported an increase in pediatric T1D diagnoses during the early phase of the pandemic[9].

This temporal overlap led to speculation that SARS-CoV-2 might contribute to disease onset. However, more recent and methodologically robust studies including both mechanistic and population-level analyses have not consistently supported a direct causal link or a sustained increase in incidence[10,11].

Attention has also turned to clinical severity at presentation. Diabetic ketoacidosis (DKA), the most serious acute complication of T1D, has been reported more frequently and more severely in children during the pandemic[12-16]. However, many of these reports lacked laboratory confirmation of SARS-CoV-2 infection, making it unclear whether this pattern reflects viral effects or broader healthcare disruptions, such as delays in care, reduced access to medical services, and parental hesitancy during lockdowns[15,16].

This prospective multicenter study evaluated the relationship between SARS-CoV-2 infection and the clinical presentation of T1D in children, focusing on DKA frequency and severity at diagnosis. In addition, the study aimed to determine the overall prevalence of SARS-CoV-2 exposure in this population. Unlike most previous investigations, which have primarily relied on retrospective or epidemiological data, this study assessed infection status at diagnosis using both polymerase chain reaction (PCR) and comprehensive serological testing.

MATERIALS and METHODS

Study Design and Setting

This prospective multicenter study was conducted from April 1, 2021, to April 1, 2022, at three tertiary care centers in Türkiye: Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Trakya University Medical Faculty Hospital, and Gazi University Medical Faculty Hospital. The studies involving human participants were reviewed and approved by the Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee, Türkiye (no.: HNEAH-KAEK 2020/KK/21, date: 12.10.2020). Informed consent was also obtained from the participating patients or their parents.

Study Population

A total of 133 children aged 1 to 18 years with newly diagnosed T1D were enrolled in this prospective multicenter study. The diagnosis and classification of DKA, including its severity, were based on the International Society for Pediatric and Adolescent Diabetes 2022 guidelines. DKA was defined by a plasma glucose level >200 mg/dL, the presence of ketonemia and/or ketonuria, and a venous pH <7.30 or a serum bicarbonate level <18 mmol/L. DKA severity was classified as mild (venous pH <7.30 or serum bicarbonate <18 mmol/L), moderate (venous pH <7.20 or serum bicarbonate <10 mmol/L), or severe (venous pH <7.10 or serum bicarbonate <5 mmol/L). Children with a history of chronic illness, immunosuppressive therapy, or steroid use were excluded from the study. Notably, none of the participants had received COVID-19 vaccination, ensuring that antibody positivity reflected natural infection. To explore the association between SARS-CoV-2 infection and clinical presentation, participants were categorized into three groups: those with active COVID-19 (PCR and/or SARS-CoV-2-specific IgM antibody positivity; n=13), those with prior infection (negative for SARS-CoV-2-

specific IgM antibodies and positive for SARS-CoV-2-specific IgG antibodies; n=39), and those with no evidence of infection (negative for both SARS-CoV-2-specific IgM and IgG antibodies; n=81).

Laboratory Evaluation

At the time of diagnosis, all patients underwent a comprehensive biochemical evaluation, including HbA1c, C-peptide, and diabetes-related autoantibodies (anti-glutamic acid decarboxylase, anti-islet cell, and anti-insulin antibodies). In addition, SARS-CoV-2 infection status was evaluated using both molecular and serological methods.

PCR

Nasopharyngeal swab samples were collected from all patients at admission and tested for SARS-CoV-2 using reverse transcription-PCR.

Serological Testing

Venous blood samples were collected at diagnosis and again 21 days later (IgG only). SARS-CoV-2 IgM and IgG antibody levels were measured at diagnosis. Serum samples were centrifuged at 400 x g for 10 minutes and stored at -80 °C until analysis.

IgM Assay

SARS-CoV-2–specific IgM antibodies were measured using the 6R87 chemiluminescent microparticle immunoassay (CMIA) on the Abbott Architect i2000SR platform. This assay detects antibodies targeting the nucleocapsid (N) protein of SARS-CoV-2. According to the manufacturer's guidelines, an index (S/C) value of ≥1.0 was considered positive, indicating recent or active infection[17].

IgG Assay

SARS-CoV-2 IgG antibodies were assessed using the 6R86 CMIA (Abbott Architect), which also targets the N protein of the virus. Test results were reported as a signal-to-cutoff (S/C) ratio, with values ≥1.4 interpreted as positive, indicating previous exposure or infection[18].

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Chicago, IL, USA).As this was an exploratory prospective observational study, no formal a priori sample size calculation was performed; we aimed to enroll all consecutive eligible patients diagnosed during the study period. The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed variables were analyzed using one-way ANOVA, while non-normally distributed variables were compared using the Kruskal-Wallis test. A p-value <0.05 was considered statistically significant. Pairwise comparisons between multiple groups were adjusted using the Bonferroni correction.

RESULTS

A total of 133 participants were included in the study. To examine the association between SARS-CoV-2 infection and clinical presentation, participants were categorized into three groups: those with active COVID-19 (n=13), those with a prior infection (n=39), and those with no evidence of infection (n=81). The mean ages of the three groups were 11.59±4.78, 9.34±4.19, and 8.44±4.35 years, respectively, with no statistically significant difference observed among the groups (p=0.056). The sex distribution was similar across the three groups, with females comprising 6/13 in the active infection group, 24/39 in the prior infection group, and 43/81 in the no-infection group (p=0.548). No statistically significant differences were observed between the groups in height, weight, body mass index, or other anthropometric parameters (all p>0.05; Table 1). Likewise, HbA1c levels, C-peptide concentrations, and the number of positive islet autoantibodies did not differ significantly among the three groups(all p>0.05; Table 1). The overall seropositivity rate for SARS-CoV-2 (IgM and/or IgG) was 39% (n=52). At diagnosis, 13 patients tested positive by PCR and/or IgM testing and were classified as having an active infection. Of these, 11 had positive PCR results, and 4 exhibited fever and elevated acute-phase reactants consistent with COVID-19. Among the 39 patients with isolated IgG positivity with negative IgM, 17 reported a personal or household history of COVID-19. The remaining 81 patients had no clinical or serological evidence of SARS-CoV-2 infection (Table 2). SARS-CoV-2 IgM antibody positivity differed significantly among the three groups; all pairwise comparisons were significant (p<0.001). Comparative analysis of SARS-CoV-2 IgG antibody positivity across the three groups demonstrated a statistically significant overall difference (p<0.001). In post-hoc pairwise analyses, no statistically significant difference was observed between the active infection and prior infection groups (p=0.413); however, the no-infection group showed a statistically significant difference compared with both groups (p<0.001). SARS-CoV-2 IgG antibody positivity measured on day 21 was concordant with overall IgG antibody positivity.

Follow-up serological testing on day 21 confirmed sustained IgG positivity in patients with prior or active COVID-19. In all groups, DKA was the most common presentation at the time of T1D diagnosis. The

frequency of DKA at presentation was 76.9% (10/13) in patients with active COVID-19, 66.6% (26/39) in patients with a prior history of COVID-19, and 54.3% (44/81) in patients with no evidence of infection. While DKA was more common among those with confirmed or previous SARS-CoV-2 exposure, the difference did not reach statistical significance (p=0.240) (Table 3). Severe DKA was the most frequent presentation in all groups; however, no statistically significant difference in severity was found between them (p=0.162) (Table 4).

Table 1. Demographic characteristics of study groups.

	Active COVID-19 + T1DM (n=13)	Past COVID-19 + T1DM (n=39)	Non-COVID-19 + T1DM (n=81)	p
Age	11.59±4.78	9.34±4.19	8.44±4.35	0.056$^{\chi}$
Gender (M/F)	7/6	15/24	38/43	0.548$^{\mu}$
Height (cm)	147.26±27.39	136.56±28.52	130.05±24.98	0.068$^{\chi}$
Height SDS	0.16±1.18	0.31±1.16	0.21±1.21	0.513$^{\chi}$
Weight (kg)	45.52±26.94	32.57±14.77	31.04±15.89	0.181$^{\chi}$
Weight SDS	-0,24±1.65	-0.45±0.99	-0.05±1.24	0.388$^{\chi}$
BMI	18.83±5.74	16.47±2.59	16.93±3.41	0.598$^{\chi}$
BMI SDS	-0.63±2.00	-0.75±1.41	-0.31±1.45	0.315$^{\chi}$
HbA1c	12.12±1.60	12.77±2.41	12.50±2.55	0.681*
C-peptide	0.64±0.70	0.49±0.37	0.65±0.62	0.495$^{\chi}$
Islet autoantibody positivity (≥1), n/N (%)	88.9%	77.8%	78.5%	0.750$^{\mu}$

BMI: Body mass index, SDS: Standard deviation score, *: One-way ANOVA test, $^{\chi}$: Kruskal Wallis test, $^{\mu}$: Chi-square test, HbA1c: Glycated hemoglobin, COVID-19: Coronavirus disease-2019, T1DM: Type 1 diabetes mellitus

Table 2. Antibody values at diagnosis and postdiagnosis 21. day of study groups.

	Active COVID-19 + T1DM (n=13)	Past COVID-19 + T1DM (n=39)	Non-COVID-19 + T1DM (n=81)	p	p_1	p_2	p_3
IgM	8.20±14.03	0.27±0.24	0.14±0.17	<0.001^{c}	<.001^{c}	<0.001^{c}	0.001^{c}
IgG	3.67±2.69	3.20±2.77	0.16±0.33	<0.001^{c}	0.413$^{\chi}$	<0.001^{c}	<0.001^{c}
IgG (21.day)	3.78±2.47	3.97±1.96	0.16±0.32	<0.001^{c}	0.794$^{\chi}$	<0.001^{c}	<0.001^{c}

χ; Kruskal Wallis test, p_1; COVID-19 + T1DM group vs. COVID-19 before T1DM group, p_2; COVID-19 + T1DM group vs. Non COVID-19 + T1DM group, p_3; Non-COVID-19 + T1DM group vs. COVID-19 before T1DM group. p_1, p_2, p_3; Bonferroni adjustment was applied in pairwaise comparison
COVID-19: Coronavirus disease-2019, T1DM: Type 1 diabetes mellitus, Ig: Immunoglobulin

Table 3. The number of patients demonstrating clinical features of the study groups at diagnosis.

	Active COVID-19 + T1DM (n=13)	Past COVID-19 + T1DM (n=39)	Non-COVID-19 + T1DM (n=81)	p
DKA	10 (% 76.9)	26 (%66.6)	44 (%54.3)	0.240$^{\mu}$
Hyperglycemia	3 (% 23.0)	7 (%17.9)	17 (%20.9)	
Ketosis	0	6 (%15.3)	20 (%24.6)	

DKA: Diabetic ketoacidosis, $^{\mu}$: Chi-square test, T1DEM: Type 1 diabetes mellitus, COVID-19: Coronavirus disease-2019

Table 4. The clinical grading of diabetic ketoacidosis (DKA) patients of study groups at diagnosis.				
	Active COVID-19 + T1DM (n=10)	**Past COVID-19 + T1DM (n=26)**	**Non-COVID-19 + T1DM (n=44)**	**p**
Mild	2 (%20)	4 (% 15.3)	17 (%38.6)	0.162[µ]
Moderate	4 (%40)	10 (%38.4)	8 (%18.1)	
Severe	4 (%40)	12 (%46.15)	19 (%43.1)	
[µ]: Chi-square test, T1DM: Type 1 diabetes mellitus, COVID-19: Coronavirus disease-2019				

DISCUSSION

This prospective multicenter study investigated the association between SARS-CoV-2 infection and the clinical presentation of T1D, with a specific focus on DKA at diagnosis. Our findings revealed no statistically significant differences in the frequency or severity of DKA among groups stratified by SARS-CoV-2 infection status. Although DKA was numerically more frequent in children with active or prior SARS-CoV-2 exposure, these differences did not reach statistical significance, suggesting that any direct viral contribution—if present—is likely modest relative to system-level factors affecting timely access to care. Taken together, these results indicate that SARS-CoV-2 infection does not appear to influence the initial severity of T1D, supporting prior observations that indirect consequences of the pandemic may have had a more substantial impact on disease presentation[11,19,20].

Early in the pandemic, studies such as those by Unsworth et al. raised concerns about a possible increase in new-onset T1D and more severe DKA in children[21,22]. While subsequent large-scale analyses, including those by Qeadan et al.[15] and D'Souza et al.[16], reported an increase in pediatric T1D incidence, they also highlighted significant methodological heterogeneity and could not definitively establish a causal relationship with SARS-CoV-2 infection. Similarly, a study from Türkiye reported an increase in the number of patients admitted to intensive care units due to DKA during the first year of the pandemic[23]. While several studies have suggested an increased severity and frequency of DKA at diagnosis in newly diagnosed T1DM patients, these findings, consistent with our study, were not statistically significant[24,25].

Hormazábal-Aguayo et al.[26], in a systematic review of global data from 55 countries over two decades, concluded that the apparent increases in T1D incidence during the pandemic were consistent with pre-existing secular trends. This review remains the most comprehensive global synthesis on the topic to date[26]. Supporting this interpretation, population-based studies from Denmark and Japan also reported no significant correlation between SARS-CoV-2 infection and new-onset T1D[27,28]. Among these, the Danish study stands out for its methodological rigor, including broad testing coverage and adjustment for key confounders. These findings collectively argue against a direct pathogenic role of the virus in altering T1D incidence[27].

Parallel experimental research has explored whether SARS-CoV-2 might contribute directly to pancreatic β-cell damage. Initial in vitro studies by Müller et al.[29] suggested possible viral entry into β-cells, but subsequent investigations, including those by van der Heide et al.[30], demonstrated only minimal and inconsistent cellular involvement. The consistent pancreatic autoantibody positivity observed in our cohort is compatible with the typical autoimmune pathogenesis of pediatric T1D. However, we acknowledge that SARS-CoV-2 has been proposed as a potential trigger of autoimmunity in susceptible individuals. Because the timing of infection relative to seroconversion and diabetes onset could not be established, our data cannot exclude an immune-mediated triggering role of the virus.

In our cohort, SARS-CoV-2 antibody seropositivity was identified in 39% of children newly diagnosed with T1D, a rate comparable to that reported in general adolescent populations, such as in Greece during the same period[31]. Although no national pediatric seroprevalence data are available for Türkiye, this rate appears consistent with background exposure levels observed in comparable settings. This finding is notably higher than those reported in studies from Spain, the United States, and Belgium, where children with new-onset T1D showed very low seroprevalence[32-34]. Such discrepancies may reflect regional variation in transmission dynamics, pandemic wave timing, or public health responses. Importantly, while previous studies typically relied on PCR or IgG serology alone, our study employed a broader virological approach, incorporating PCR, IgG, and IgM testing at the time of diagnosis, with a repeat IgG test 21 days later. This enhanced methodology likely enabled the detection of both recent and past infections, capturing a wider range of SARS-CoV-2 exposures.

Despite this detailed virological profiling, we observed high rates of severe DKA even among children without documented SARS-CoV-2 infection. These findings point to broader pandemic-related factors, such as delayed presentation, healthcare system strain, and reduced access to services, as likely contributors to worsened disease severity. Similar conclusions were drawn by Ata et al.[19] and Lawrence et al.[20], who found no significant differences in seroprevalence between T1D and control groups but attributed higher DKA severity to healthcare disruptions. Consistent with these observations, the substantial proportion of severe DKA across all groups in our cohort aligns with national PICU-based data from Türkiye demonstrating an increase in severe DKA during the pandemic, further supporting the notion that delayed presentation and healthcare system disruptions played a central role in metabolic decompensation[23].

Study Limitations

This study has some limitations. First, the relatively small sample size (particularly the small number of patients with active SARS-CoV-2 infection) may have reduced the statistical power to detect subgroup differences, particularly those related to DKA severity. Second, pubertal (Tanner) staging was not systematically recorded; therefore, analyses stratified by pubertal status could not be performed. Third, although serological testing was performed at two time points, the exact timing of infection relative to T1D onset could not be established, limiting causal inference. Although multicenter design of the study, it is based on data from a single country, which may limit the generalizability of the findings globally. Finally, data on socioeconomic status, healthcare access, and time to diagnosis, which are known to influence DKA risk, were not available.

CONCLUSION

In conclusion, our findings do not support a significant association between SARS-CoV-2 infection and the frequency or severity of DKA at T1D onset. Despite this detailed virological profiling, we observed high rates of severe DKA even among children without documented SARS-CoV-2 infection. The patterns observed across all groups suggest that healthcare disruptions during the pandemic were likely more influential than the infection itself. These findings support the need for sustained public messaging about early diabetes symptoms and safeguarding timely pediatric access to emergency and primary care pathways during public health crises, to mitigate preventable severe DKA at diagnosis. Prospective, population-based studies with larger cohorts and system-level data are needed to fully elucidate the multifactorial impact of global health emergencies on pediatric T1D.

Ethics

Ethics Committee Approval: The studies involving human participants were reviewed and approved by the Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee, Türkiye (no.: HNEAH-KAEK 2020/KK/21, date: 12.10.2020).

Informed Consent: Informed consent was also obtained from the participating patients or their parents.

Footnotes

Author Contributions

Surgical and Medical Practices: M.N.H., F.T.K., H.C.E., M.Y., A.B., Concept: M.N.H., F.T.K., H.C.E., A.O.C., D.D.B., F.K.I., P.C., Design: M.N.H., F.T.K., A.O.C., M.Y., A.B., Data Collection and/or Processing: M.N.H., H.Y.K., Z.K., D.D.B., F.K.I., P.C., Analysis or Interpretation: M.N.H., H.C.E., H.Y.K., Z.K., M.Y., P.C., Literature Search: M.N.H., A.O.C., H.Y.K., Z.K., A.B., Writing: M.N.H., F.T.K., H.C.E., F.K.I.

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