Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.21284

The Examination of the Relationship Between COVID-19 and New-Onset Type 1 Diabetes Mellitus in Children

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What is already known on this topic?

- *Viral infections take a part in type 1 diabetes mellitus (T1D) development, causing either direct cytolytic effect and gradual beta cell destruction or initiate immune reactions.*
- *The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes acute respiratory distress, but the relation with other systems is not fully understood.*

What this study adds on this topic?

- *The rates of diabetic ketoacidosis (DKA) and severe DKA were similar in coronavirus disease 2019 pandemic and prepandemic periods.*
- *There was no finding suggesting that SARS-CoV-2 have a role in T1D pathogenesis.*

ABSTRACT

Objective: This study aimed to evaluate presentations of new-onset type 1 diabetes mellitus in a pediatric cohort during the coronavirus disease 2019 pandemic.

Materials and Methods: This study was designed as a single-center, descriptive, cross-sectional retrospective study. The patients diagnosed with new-onset type 1 diabetes mellitus between April 1, 2020, and April 1, 2021, were included in the study. The rate of severe acute respiratory syndrome coronavirus 2 polymerase chain reactivity-positivity was investigated. The pandemic period was compared with the same period of the pre-pandemic 2 years in terms of number of new-onset type 1 diabetes mellitus patients, rate of presentation with diabetic ketoacidosis, and degree of diabetic ketoacidosis severity.

Results: In total, 56 patients were diagnosed with type 1 diabetes mellitus during the pandemic and 2 (3.57%) of them tested positive for severe acute respiratory syndrome coronavirus 2 polymerase chain reaction. The number of new-onset type 1 diabetes mellitus patients was 39 in 2019 and 39 in 2018. The rate of presentation with diabetic ketoacidosis was similar in the pandemic period compared to the pre-pandemic periods (53.5% in 2020 vs. 56.4% in 2019 and 53.8% in 2018; $P = .94$). The proportion of severe diabetic ketoacidosis was also similar in all years, respectively (43.3% in 2020 vs. 45.4% in 2019 and 47.6% in 2018; $P = .95$).

Conclusion: We reported only 2 cases that tested positive for severe acute respiratory syndrome coronavirus 2among the new-onset type 1 diabetes mellitus patients during the pandemic. Although we found an increase in the number of new-onset type 1 diabetes mellitus cases by comparing with prepandemic period, rates of diabetic ketoacidosis and severe diabetic ketoacidosis were similar. There was no finding to suggest that severe acute respiratory syndrome coronavirus 2taking a part in type 1 diabetes mellitus pathogenesis. Since the development of type 1 diabetes mellitus is a long process, prospective studies are needed to investigate the long-term effects of severe acute respiratory syndrome coronavirus 2.

Keywords: COVID-19, new-onset diabetes, SARS-CoV-2, type 1 diabetes

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a common childhood disease that occurs as a result of autoimmune damage to islet (β) cells of the pancreas and is characterized by insulin deficiency and hyperglycemia. The most common symptoms of T1D include polyuria, polydipsia, weight loss, weakness, and fatigue.[1] The incidence of T1D varies in different countries, different geographical regions of the country, and different ethnic groups. Environmental, genetic, and socioeconomic factors play an important role in the occurrence of this difference.[2] Viral infections may cause either direct cytolytic effect and gradual β cell destruction or initiate immune reactions.[1] Congenital Rubella syndrome is a known condition associated with the development of diabetes.[3] Therewithal, Coxsackievirus B1 infection is associated with the

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Received: September 30, 2021
Accepted: November 13, 2021

Cite this article as: Donbaloğlu Z, Tuhan H, Tural Kara T, et al. The examination of the relationship between COVID-19 and new-onset type 1 diabetes mellitus in children. *Turk Arch Pediatr.* 2022;57(2):222-227.

development of both islet autoimmunity and T1D.[4] The role of other viruses mentioned such as cytomegalovirus, mumps, influenza, rotavirus, and H1N1 is not fully understood in the development of T1D.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA viruses from the betacoronavirus family.[5] The first coronavirus disease 2019 (COVID-19) case was identified in Wuhan in China in December 2019, and then, cases began to be seen in many countries. Mortality and morbidity were increased, and the World Health Organisation (WHO) declared COVID-19 as a pandemic in March 2020 which is the same month the first case was seen in Turkey. During COVID-19 pandemic, an increase in the number of children with newly diagnosed T1D has been reported.[6-8] According to several reports from regions heavily impacted by the pandemic suggest that there is a relationship between diabetic ketoacidosis (DKA) severity and COVID-19 infection.[6-10] Because data on the association between new-onset T1D and COVID-19 are limited especially in children, it is unclear whether there is a true increase in the T1D incidence or rather an exacerbation of the disease presentation.

This study aimed to evaluate a Turkey's center's experience of presentations of new-onset T1D in a pediatric cohort during the COVID-19 pandemic period (April 2020 to April 2021) compared to pre-pandemic presentations in the same periods of the previous 2 years.

MATERIALS AND METHODS

Study Design and Data Collection

This study was designed as a single-center, descriptive, cross-sectional retrospective study. The patients diagnosed with new-onset T1D in Akdeniz University Faculty of Medicine Hospital Pediatric Endocrinology Clinic between April 1, 2020, and April 1, 2021, were included in this study. During this 1-year period, there were pandemic restrictions in our country. Our hospital served as a reference hospital in the Mediterranean Region, and patients from different provinces were applied to our hospital which continued to admit patients during the pandemic. The demographic, clinical, and laboratory characteristics of the patients were retrieved retrospectively from the database records of our hospital. The study period (April 1, 2020, to April 1, 2021) compared to the same periods of the 2 years pre-pandemic. The patients were evaluated in 3 groups as group 1 (pandemic period), group 2 (April 1, 2020, to April 1, 2019 period), and group 3 (April 1, 2019, to April 1, 2018 period). The number of new-onset T1D patients, the rate of presentation with DKA, and the degree of DKA severity were investigated in all groups and compared with each other.

Definitions and Diagnostic Procedures

In total, 56 patients younger than 18 years were included in the study, who are diagnosed with new-onset T1D in our hospital during the COVID-19 pandemic. The diagnosis of patients with T1D according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) 2018 guideline[11] was determined. The blood glucose concentration on admission, c-peptide, glycosylated hemoglobin $A1_c$ ($HBA1_c$), initial venous blood gas pH and bicarbonate, T1D-associated autoantibody status [presence of at least 1 positive result of antibodies to glutamic acid decarboxylase (anti-GAD), islet cell antibodies, and insulin antibodies] were recorded. Whether the patient had DKA on admission was determined. Diabetic ketoacidosis was defined as blood glucose concentration > 200 mg/dL, venous pH < 7.3 or bicarbonate < 15 mmol/L, and presence of ketonemia or ketonuria on presentation. Severity of DKA is classified as mild DKA (pH 7.20-7.30 or bicarbonate: 10-15 mmol/L), moderate DKA (pH 7.20-7.10 or bicarbonate: 5-10 mmol/L), and severe DKA (pH <7.10 or bicarbonate: <5 mmol/L) according to ISPAD 2018 guideline.[11] The results of SARS-CoV-2 real-time polymerase chain reaction (PCR) test which were taken within the first 24 hours of hospitalization from nasopharyngeal swab samples were recorded through the digital database. Age in diagnosis, gender, body weight, weight standard deviation score (SDS), height, height SDS, body mass index (BMI), and BMI SDS of the patients were also recorded. Family history was investigated in terms of T1D. The symptoms of polyuria, polydipsia, loss of appetite, abdominal pain, nocturia, weight loss, dyspnea, fever, nausea, vomiting, and lethargy were examined, and the time elapsed from the onset of symptoms was recorded.

Ethics

Ethics committee permission was obtained from Ethics committee of Akdeniz University (Approval date: August 6, 2021, Number: 70904504/502), and the study was managed in accordance with the Helsinki Criteria. As it was a retrospective study, no further ethical approval was taken from the patients.

Statistical Analysis

The Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA) program was used for statistical analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements were given as median [interquartile range (IQR)] or mean ± SD. Pearson chi-square and Fisher's exact tests were used to compare the categorical variables. The Shapiro–Wilk test was used to determine whether the parameters in the study showed normal distribution or not. In the comparison of continuous measurements between groups, distributions were controlled, and the Mann–Whitney *U* test was used for parameters that did not show normal distribution. A *P* value of <.006 obtained in the Mann–Whitney *U* test was considered significant (Bonferroni correction). A *P* value of <.05 was considered statistically significant.

RESULTS

Results of Pandemic Period

In total, 56 children presented with new-onset T1D during the pandemic period. The mean age at the time of diagnosis was 9.44 ± 4.09 (2.27-17.9) years, and 26 (48.2%) of them were female and 29 (51.8%) were male. A familial history of T1D was present in 2 (3.57%) patients. The median duration of symptoms was 10 (23.2) days. The median body weight SDS was 0 (1.52), the median height SDS was 0.30 (0.96), and the median BMI SDS was −0.34 (2.08). At the initial presentation, laboratory findings were found to be as follows: mean blood glucose concentration: 402.6 ± 154.2 mg/dL, mean $HbA1_c$: 13.1 ± 2.3, mean pH: 7.21 ± 0.19, and median bicarbonate: 13.3 (15.5) mmol/L (Table 1). The most frequent complaint during the pandemic

Table 1. The Clinical and Laboratory Characteristics of New-Onset Type 1 Diabetes Mellitus Patients Diagnosed During COVID-19 Pandemic

Age (years)	9.44 ± 4.09
Sex (M, %)	29 (51.8)
Weight SDS	−0.13 ± 1.1
Height SDS	0.45 ± 1.07
BMI SDS	−0.58 ± 1.46
Family history of T1D (%)	6 (10.7)
Duration of symptoms (day)	10 (23.2)
Plasma glucose (mg/dL)	402.6 ± 154.2
C-peptide (ng/mL)	0.37 (0.46)
HbA1c (mmol/mol, %)	13.1 ± 2.3
pH	7.21 ± 0.19
Bicarbonate (mmol/L)	13.0 ± 7.75
COVID-19 PCR positivity (%)	2 (3.57)

Data are given as mean ± SD or median (IQR).
IQR, interquartile range; M, Male; SDS, standard deviation score; T1D, type 1 diabetes mellitus; HBA1c, glycosylated hemoglobin $A1_C$, PCR, polymerase chain reaction.

period was polyuria (92.9%). Other complaints were loss of appetite, abdominal pain, nocturia, weight loss, dyspnea, fever, vomiting, nausea, and lethargy (Table 2). Thirty (53.5%) patients presented with DKA. Of the patients with DKA, 9/30 (30%) had mild DKA, while 8/30 (26.7%) had moderate DKA, and 13/30 (43.3%) had severe DKA.

Comparison of Pandemic and Pre-Pandemic Period

The number of patients who were diagnosed with new-onset T1DM was 39 in group 2 and group 3 in the prepandemic period, while it was 56 during the pandemic period. There was an increase in the number of new-onset T1D. The DKA rate was found as 53.5% (30/56), 56.4% (22/39), 53.8% (21/39) in groups 1, 2, and 3, and there was no significant difference in pandemic and pre-pandemic period ($P = .94$). Severe DKA rate was also similar with the results of 43.3% (13/30), 45.4% (10/22), 47.6% (10/21) in groups 1, 2, and 3 ($P = .95$) (Table 3).

Characteristics of Cases with COVID-19 Infection

In total, 2 (2/56, 3%) patients were tested positive for SARS-CoV-2 PCR. First patient was a 9.6-year-old female. She was admitted to our emergency department with complaints of fever episodes, dyspnea, abdominal pain, and vomiting for

Table 2. Presenting Complaints of New-Onset Type 1 Diabetes Mellitus Patients Diagnosed During COVID-19 Pandemic

Complaint (n/%)	
Polyuria	52 (92.9)
Polydipsia	50 (89.3)
Weight loss	28 (50)
Nocturia	26 (46.4)
Abdominal pain	23 (41.1)
Absence of appetite	22 (39.3)
Dyspnea	13 (23.2)
Fever	10 (17.9)
Nausea or vomiting	9 (16.1)
Lethargy	3 (5.4)

Data are given as n (%).

Table 3. The Number of New-Onset Type 1 Diabetes Mellitus Patients and Rate of Diabetic Ketoasidosis by Years

	Group 1 (April 2020 to April 2021)	Group 2 (April 2019 to April 2020)	Group 3 (April 2018 to April 2019	*P*
Number, n	56	39	39	
DKA (n/%)	30 (53.5)	22 (56.4)	21 (53.8)	.94[a]
Mild	9 (30.0)	6 (27.3)	6 (28.5)	.99[a]
Moderate	8 (26.7)	6 (27.3)	5 (23.9)	.94 [a]
Severe	13 (43.3)	10 (45.4)	10 (47.6)	.95 [a]
pH	7.26 (0.19)	7.21 (0.31)	7.24 (0.29)	.97[b]
Bicarbonate (mmol/L)	13.3 (15.5)	9.3 (11.9)	10.2 (13.1)	.33[b]

[a]Kruskal–Wallis test; [b]Chi-square test. Data are given as median ± IQR. DKA, diabetic ketoacidosis; IQR, interquartile range.

3 days while she already had polyuria, polydipsia, nocturia, and weight loss for 1 month. On physical examination, she had Kussmaul respiration pattern and respiratory sounds were normal. Laboratory testing revealed severe DKA with blood gas pH 6.9 and bicarbonate 1.6 mmol/L, blood glucose 431 mg/dL, a reduced serum C-peptide level of 0.18 ng/mL (normal range, 1.1-5 ng/mL), and $HbA1_c$ 14.8%, as well as positive urinary ketones and glucosuria. The liver and renal function tests and hemoglobin concentration were normal. Anti-GAD was found to be positive as 12.04 IU/mL (0-10). The patient was diagnosed with T1D. She required treatment in the pediatric intensive care unit (PICU) for 2 days for recompensating DKA and was administered intravenous insulin therapy according to the ISPAD guidelines.[11] On day 3, she was transferred to COVID-19 pandemic clinic and subcutaneous insulin therapy was initiated. No special treatment was given for COVID-19. She recovered without complications and was cdischarged from the hospital on day 7. Video-telemedicine was mostly used for insulin-dependent diabetes mellitus management.

Second patient was $17^{11/12}$-year-old girl who was referred from an external center to the pediatric emergency department of our hospital with complaints of fever, respiratory distress, and vomiting for 4 days. She also had complaints of polydipsia, polyuria, and weight loss for 2 months. It was learned that the SARS-CoV-2 PCR test, which was performed in an external center, was found to be positive in the whole family 5 days ago and they were quarantined at home. She had 22-year-old sister who had been followed up with T1D for 14 years. On physical examination, her consciousness was lethargic, and there was deterioration in general condition. She had no fever. Laboratory work-up was notable for severe DKA with blood gas pH 6.74 and bicarbonate 2.8 mmol/L, blood glucose 540 mg/dL, a reduced serum C-peptide level of 0.20 ng/mL (normal range, 1.1-5 ng/mL), $HbA1_c$ 16.8%, creatinine 1.26 mg/dL (0.5-1.1), and BUN 15 mg/dL (9-23). The urinary ketone and glucose were positive. Anti-GAD was found to be positive as more than 120 IU/mL (0-10), and she was diagnosed with T1D. She tested positive for SARS-CoV-2 PCR and was isolated in PICU. Intravenous insulin, fluid therapy, favipiravir, ceftriaxone, low molecular weight heparin, and acetylsalicylic acid treatments were initiated. Infiltration was detected in the chest radiography of the patient who developed fever on the second day

of hospitalization. Acute phase reactants were increased and lymphopenia developed. Ejection fraction was measured as 60% on echocardiography and acute renal failure developed. Since the presence of persistent fever, 2-system involvement, and lymphopenia, the case was considered as multisystemic inflammatory syndrome in children according to WHO diagnostic criteria.[12] Intravenous immunoglobulin, steroid, plasmapheresis, and anakinra treatments were administered. On the sixth day of admission, ketoacidosis was improved, and subcutaneous insulin treatment was initiated. The COVID-19 treatment and insulin-dependent diabetes managing education were completed, and the patient was discharged in a good condition.

DISCUSSION

The COVID-19 pandemic has caused a health crisis and death worldwide. The lockdown period, changes in health priorities, and problems in accessing routine health services during the pandemic provided the patients with chronic diseases being at higher risk, and studies have started to examine the relationship between chronic diseases and COVID-19. The relationship of T1D, which is an important chronic disease of childhood, with COVID-19 was also wondered. First study evaluating the association between T1D and COVID-19 in the young population (mean age, 20.9 years) was reported by a study in the United States, and the COVID-19 positivity was reported as 10% in new-onset T1D patients.[13] When they also evaluated the cases both newly and previously diagnosed with T1D together, they also reported that the most prevalent adverse outcome within COVID-19-positive patients was DKA (45.5%). The rate of DKA during the pandemic was not compared with previous years in this study. After that, the first study evaluating only pediatric cases was published in England, and Unsworth et al[6] have reported that there was an increase in the number of new-onset T1D patients during the pandemic period when compared with 5 years prepandemic and the rate of DKA was 70% among these patients. In their study, 5 of 30 new-onset T1D cases were COVID-19-positive and 4 of them had DKA on admission. In our study, there were only 2 COVID-19-positive patients among 56 new-onset T1D cases. Both patients presented with severe DKA and needed treatment in PICU similar to the cases of Unsworth's study. In contrast, a study from Italy reported that there was a 26% reduction in new-onset T1D cases during pandemic when compared with previous year.[10] The rate of DKA was constant in pandemic and prepandemic periods similar to our results, but the rate of severe DKA was increased (36.1%-44.3%). In this study, although the low rate of COVID-19 PCR positivity (1/160) among the newly diagnosed T1D cases is consistent with our study, this rate is not fully reliable since COVID-19 PCR test was not taken from cases who did not show obvious COVID-19 symptoms. They discussed that lower exposure to seasonal viruses, such as enteroviruses, adenoviruses, and influenza viruses which are known precipitating factors for T1D with the quarantine, results in decrease in the number of new-onset T1D cases. Additionally, as reported in the study of Scaramussa et al.[14] significantly reduced pediatric emergency department access during the pandemic, most likely due to the fear of infection, might have been the reason for increased proportion of severe DKA. In a study from Finland where the incidence of COVID-19 is relatively low, it was reported that there was an increase in the number of new-onset T1D and the rate of severe DKA.[9] They similarly discussed the avoidance of hospitals due to the fear of contamination as a reason rather than the direct diabetogenic effect of SARS-COV-2 since there was no COVID-19-positive case in their study group. An increase in both the rates of DKA and severe DKA during the pandemic was also reported in Germany and Turkey.[7,8] Kamrath et al[8] underlined that the rate of DKA increased simultaneously with the first wave of the increasing number of COVID-19 cases but paradoxically continue to increase after the first wave. This might be an example of the fact that the fear of contamination has had a persistent effect on the population and delayed admission to the hospital on time. In another study conducted out of 216 German pediatric diabetes centers, it was reported that the T1D incidence in 2020 remained within the predicted range.[15] It follows already an increasing trend observed between 2011 and 2019 without up- or downward deviation, indicating no short-term influence of the COVID-19 pandemic. Thus, they speculated that strong direct diabetogenic effects of COVID-19 seem very unlikely.[15] We also observed an increase in the number of new-onset T1D patients compared to previous 2 years. Regardless of the pandemic, increasing T1D incidence worldwide might be the reason for this situation. In a systematic review published in 2020 from 1202 located articles, the results showed that both incidence and prevalence of T1D are already increasing in the world (incidence: 15 per 100 000 people, prevalence: 9.5%).[16] Additionally, the increasing number of new-onset T1D cases might have been caused by the fact that some centers in our region were turned into COVID-19 reference hospitals and more non-covid patients were directed to our hospital such as new-onset T1D patients.

Acar et al[17] reported that severe ketoacidosis has been reported to be 10%, over a period of 5 years in Turkey. Severe DKA rate was 23.2% (13/56) in all new-onset T1D cases in our study. Although it was higher compared to this study, it was similar with previous years in our hospital and also with another study from Turkey in pandemic period (20.2%, 15/74).[7] When we measured the rate of severe DKA among the cases presented with DKA (43.3%), it was similar to the results of the study from Italy (44.3%).[10]

Although the high $HbA1_c$ level in our patients indicates that diabetes is not in recent, some studies have reported very high levels of $HbA1_c$ in patients with DKA, regardless of the duration of diabetes.[18,19] But additionally, the duration of symptoms in COVID-19-positive cases was also long (1 and 2 months) in our study. It was thought that COVID-19 positivity at the time of diagnosis with T1D did not have a direct diabetogenic effect, but there is always a possibility that COVID-19 infection has accelerated the prediabetic process. Hollstein et al[20] have reported a patient diagnosed with new-onset T1D approximately 1.5 months after COVID-19 infection. In this situation, long-term studies in which COVID-19 antibodies are investigated in newly diagnosed T1D cases are important in terms of revealing the effects of previous COVID-19 infection on the prediabetic process.

In vitro studies have shown that SARS-CoV-2 entry into human host cells requires binding to the cell surface receptor angiotensin-converting enzyme 2 (ACE2), as well as proteolytic

cleavage of the viral spike protein by transmembrane serine protease 2 (TMPRSS2).[21] Previous studies reported that ACE2 receptors are also strongly expressed in pancreatic cells of mice and humans.[21,22] Yang et al[23] reported in 2010 that SARS-CoV-1 virus may have entered pancreatic β cells via the ACE2 receptor leading to β cell damage and new-onset diabetes. Based on these knowledge, some studies, which found higher rates of new-onset T1D during the pandemic, suggested the hypothesis that SARS-CoV-2 may also cause β-cell destruction and T1D by entering pancreatic β cells via ACE2 and TMPRSS2.[6,20] But recently, Coate et al[24] examined the expression of SARS-CoV-2 entry proteins in the human pancreas and reported that ACE2 expression in the microvasculature, including islet pericytes, whereas both ACE2 and TMPRSS2 are expressed in some ducts. Conversely, neither protein was detected in β cells in vivo. These findings disprove the hypothesis of direct cytotoxic effect of SARS-Cov-2 on β cells via ACE2 and TMPRSS2.

Limitations

Since it was a retrospective study, we could only conduct the data of the SARS-CoV-2 PCR test results of the patients. The major limitation was that no antibody test was performed on the patients. Therefore, we could not catch the cases who previously had COVID-19 infection. Additionally, we only evaluated data obtained from a single center, our findings could not represent the general situation of Turkey.

CONCLUSION

We reported only 2 cases with COVID-19 infection among the 56 new-onset T1D patients during the COVID-19 pandemic. Although we found an increase in the number of new-onset T1D cases compairing with prepandemic period, rates of DKA and severe DKA were similar. With these results, there was no finding to suggest that SARS-CoV-2 taking a part in T1D pathogenesis. Since the development of T1D is a long process, prospective studies are needed to investigate the long-term effects of SARS-CoV-2.

Ethics Committee Approval: This study was approved by Ethics committee of Akdeniz University, (Approval NO: 70904504/502).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.T., Z.D.; Design – H.T., Z.D., T.T.K.; Supervision – M.P., H.T.; Resources – A.B., E.B.Ç., B.S.; Materials – H.T., Z.D.; Data Collection and/or Processing – Z.D., A.B., B.S., E.B.Ç., T.T.K.; Analysis and/or Interpretation – H.T., Z.D.; Literature Search – Z.D., H.T.; Writing Manuscript – Z.D., H.T.; Critical Review – H.T., M.P.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Mayer-Davis EJ, Kahkoska AR, Jefferies C, et al. ISPAD Clinical Practice Consensus Guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2018;19(suppl 27):7-19. [CrossRef]
2. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics*. 2014;133(4):e938-e945. [CrossRef]
3. Gale EA. Congenital rubella: citation virus or viral cause of type 1 diabetes? *Diabetologia*. 2008;51(9):1559-1566. [CrossRef]
4. Laitinen OH, Honkanen H, Pakkanen O, et al. Coxsackievirus B1 is associated with induction of β-cell autoimmunity that portends type 1 diabetes. *Diabetes*. 2014;63(2):446-455. [CrossRef]
5. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20(6):363-374. [CrossRef]
6. Unsworth R, Wallace S, Oliver NS, et al. New-onset Type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. *Diabetes Care*. 2020;43(11):e170-e171. [CrossRef]
7. 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;34(10):1303-1309. [CrossRef]
8. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents With newly diagnosed Type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA*. 2020;324(8):801-804. [CrossRef]
9. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2021. [CrossRef]
10. 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(11):2870-2872. [CrossRef]
11. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(suppl 27):155-177. [CrossRef]
12. COVID-19.2020. *WHOSBMisicaaw*.
13. Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. *Diabetes Care*. 2020;43(8):e83-e85. [CrossRef]
14. Scaramuzza A, Tagliaferri F, Bonetti L, et al. Changing admission patterns in paediatric emergency departments during the COVID-19 pandemic. *Arch Dis Child*. 2020;105(7):704-706. [CrossRef]
15. Tittel SR, Rosenbauer J, Kamrath C, et al. Did the COVID-19 lockdown affect the incidence of pediatric type 1 diabetes in Germany? *Diabetes Care*. 2020;43(11):e172-e173. [CrossRef]
16. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. *Health Promot Perspect*. 2020;10(2):98-115. [CrossRef]
17. Acar S, Gören Y, Paketçi A, et al. Changes in the frequency of diabetic ketoacidosis in type I diabetes mellitus cases at diagnosis: a fifteen-year single center experience. *JPR*. 2017;4(3):143-148. [CrossRef]
18. O Ekpebegh C, Longo-Mbenza B, Blanco-Blanco E. Glycosylated haemoglobin is markedly elevated in new and known diabetes patients with hyperglycaemic ketoacidosis. *Afr Health Sci*. 2014;14(3):526-532. [CrossRef]
19. Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic

ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68(4):533-541. [CrossRef]
20. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. *Nat Metab*. 2020;2(10):1021-1024. [CrossRef]
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280.e8. [CrossRef]
22. Roca-Ho H, Palau V, Gimeno J, Pascual J, Soler MJ, Riera M. Angiotensin-converting enzyme 2 influences pancreatic and renal function in diabetic mice. *Lab Invest*. 2020;100(9):1169-1183. [CrossRef]
23. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193-199. [CrossRef]
24. Coate KC, Cha J, Shrestha S, et al. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. *Cell Metab*. 2020;32(6):1028.e4-1040.e4. [CrossRef]