

RE: Comment On: Change in the Frequency of Diabetic Ketoacidosis in Children with Newly Diagnosed Type 1 Diabetes in the Central Anatolia Region of Türkiye Over the Years Before and After the Coronavirus Disease 2019 Pandemic: A Single-Center Experience

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We would like to thank Al-Mendalawi¹ for his interest in our study, and for providing perspective. In recent years, lots of studies and meta-analyses have been reported regarding the increased incidence of type 1 diabetes (T1D) and diabetic ketoacidosis (DKA) after the coronavirus disease 2019 (COVID-19) pandemic.

The main point stated in the article by Koca et al² is that the frequency of DKA is still at high levels at the time of admission, compared to before the pandemic. Koca et al's² study examines the long-term course of T1D admissions (ward and intensive care admissions), especially after the pandemic. Also, the cities where applications came to their region and the admission seasons were examined.

In a random-effects meta-analysis of pooled data from 15 studies including a total of 4324 children and adolescents with DKA, the incidence rate of DKA was found to be higher during the pandemic period compared to the pre-pandemic period (incidence rate ratio, 1.26; 95% CI, 1.17-1.36).³

When we carefully examine the points mentioned by the author, we see that they focus on factors that may affect the frequency of ketoacidosis at the time of admission of individuals with newly diagnosed T1D. They tried to explain these points under 3 basic headings:

(1) The relationship between T1D and COVID-19:

These factors are metabolic dysfunction, direct COVID-19-related damage, and body immune responses.

The increased frequency of newly diagnosed T1D cases and DKA during the COVID-19 pandemic has suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may also trigger T1D.⁴ Possible mechanisms of β -cell damage include virus-induced cell death, immune-mediated loss of pancreatic β cells, and damage to β cells due to infection of surrounding cells.⁴ That study examining the potential pathways by which SARS-CoV-2 affects islet β -cells highlighted that T1D can be triggered by SARS-CoV-2 through various autoimmune mechanisms, including epitope spreading, molecular mimicry, and bystander activation.⁴ Given that the development of T1D is often a chronic, long-term process, it is currently difficult to draw definitive conclusions about whether SARS-CoV-2 causes T1D. In a meta-analysis examining the risk of developing new-onset T1D in children and adolescents as a post-acute sequela of SARS-CoV-2 infection, 11220530 participants (2140897 patients with a history of the diagnosis of SARS-CoV-2 infection and 9079633 participants in the corresponding control groups) were included. Severe acute respiratory syndrome

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coronavirus-2 infection was associated with an elevation in the risk of DKA in children and adolescents compared with non-COVID-19 control groups (RR = 2.56, 95% CI 1.07-6.11, $P = .03$).⁵

- (2) Factors specific to the individual, such as parents' education levels and socioeconomic status:"

It has been shown that children's diabetes management is better in families with good socioeconomic status and where both parents live together.⁶ In our study, we did not have sufficient information in our retrospective dataset regarding socioeconomic status and family income level. Our center is a tertiary healthcare institution affiliated with the Ministry of Health. Since healthcare services in Türkiye are provided for the public benefit through the social security institution, healthcare services are provided to patients without any additional fee. The majority of patients applying to our center are from low- or middle-income families. Although the educational status of family members was not questioned, characteristics such as whether the parents were together or divorced were questioned. We can state that the parents of only 5 families (2.6%) among the children in the study group were divorced and living separately.

- (3) Factors changing in our lives with the COVID-19 vaccine, and also COVID-19 vaccine profiles of individuals with T1D. Vaccine-related changes in blood sugar regulation or differences in antibody response in vaccinated individuals:

In our study, individuals diagnosed with T1D during and after the pandemic did not have a history of COVID-19 vaccination. These data were obtained from the patient's vaccination history records, which were collected during the first admission.

A study was conducted between April 2021 and 2022 by examining the presence of SARS-CoV-2 and T1DM-specific antibodies in a group of T1D. In the patient group with positive SARS-CoV-2 serology, a higher percentage of detectable IA-2A antibodies, more children with antibody positivity for all 3 identified islet autoantibodies (GADA, ICA, and IA-2A), and higher mean HbA1c values were detected. There was no difference between the 2 groups in terms of the presence and severity of DKA.⁷ In a study comparing 2-year follow-up before and after the pandemic in China, during 2017-2022, the rate of patients presenting with DKA was observed to fluctuate from year to year and peaked in 2020, the first year of COVID-19. The frequency of DKA was not found to be significantly higher in the 2020-2022 group compared to the 2017-2019 group (60.23% vs. 55%; $P = .521$).⁸

However, the points that the authors draw attention to are the factors that may affect the high frequency of DKA. Here, the points highlighted were not evaluated because the dataset was retrospective and these features were not distributed homogeneously in the study group. Moreover, in the presence of sufficient data, the issue of factors affecting the frequency of DKA in individuals with T1D could be the subject of separate research.

We believe that clearer interpretations can be made through long-term studies on the role of viral infections such as COVID-19 in the pathogenesis of T1D.

Declaration of Interests: The authors have no conflicts of interest to declare.

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