Short Communication

Anissa Messaaoui*, Lucia Hajselova and Sylvie Tenoutasse

Anti-SARS-CoV-2 antibodies in new-onset type 1 diabetes in children during pandemic in Belgium

https://doi.org/10.1515/jpem-2021-0289
Received April 22, 2021; accepted June 28, 2021;
published online July 19, 2021

Abstract

Objectives: Questions are emerging concerning the long-term consequences of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, as a possible increase in type 1 diabetes. This study aims to describe the prevalence of anti-SARS-CoV-2 antibodies in children developing type 1 diabetes during this pandemic in Belgium.

Methods: This observational study included children and adolescents (under 16 years) admitted with new-onset type 1 diabetes. SARS-CoV-2 serology was taken within the first month of diabetes.

Results: Of the 75 participants, anti-SARS-CoV-2 antibodies were positive in 20% of patients. They had an increased bicarbonate and base excess at diagnosis. Overall 29% of patients presented diabetic ketoacidosis at diagnosis and 9% of them were positive for anti-SARS-CoV-2 antibodies. Insulinoma-associated protein 2 antibodies positivity had significantly higher frequencies in children without anti-SARS-CoV-2 antibodies (49 (81%) vs. 5 (33%), p=0.038). Nine (15%) patients, initially seronegative, have developed anti-SARS-CoV-2 antibodies between the two samples (mean time 8 ± 4 weeks).

Conclusions: The prevalence of anti-SARS-CoV-2 antibodies in children with newly diagnosed type 1 diabetes (20%) is similar to that found in children without diabetes in Belgium, a country severely affected by this pandemic.

***Corresponding author: Anissa Messaaoui**, MD, Diabetology Clinic, HUDERF, 15 Jean-Joseph Crocq Avenue, 1020 Brussels, Belgium, Phone: +32 2 477 33 84, E-mail: anissa.messaaoui@huderf.be. https://orcid.org/0000-0002-0331-8589
Lucia Hajselova and Sylvie Tenoutasse, Diabetology Clinic, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles (ULB), Brussels, Belgium, E-mail: lucia.hajselova@huderf.be (L. Hajselova), sylvie.tenoutasse@huderf.be (S. Tenoutasse)

Keywords: SARS-CoV-2 antibodies; serology; type 1 diabetes.

Type 1 diabetes is characterized by autoimmune β cells destruction [1]. A model, proposed in 1986, suggests that individuals are born with varying genetic predispositions to diabetes and that the autoimmune reaction is triggered by environmental factors [2]. Infections are a well-known environmental factor for autoimmunity [3] and studies have implicated viral infections in the development of type 1 diabetes [1]. In 2017, the TEDDY study – The Environmental Determinants of Diabetes in the Young – showed increased autoimmunity against β cells in patients with recent respiratory tract infections, including coronavirus infections [4].

Since the end of 2019, a pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is developing worldwide [5]. The treatment is still monopolizing most of the medical community until the susceptible population can be vaccinated. However, questions are emerging concerning the long-term consequences of such a pandemic, as a possible increase in type 1 diabetes [6].

In this context, this study aims to describe the prevalence of anti-SARS-CoV-2 antibodies in Belgian children developing type 1 diabetes during the pandemic. Inclusion criteria were all patients admitted with new-onset type 1 diabetes to the Diabetes Clinic of the Queen Fabiola University Children's Hospital between March 2020 and February 2021. The diagnosis of type 1 diabetes is made according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) [7].

Laboratory measurements were blood glucose by the hexokinase method, glycated hemoglobin value by high-pressure cation exchange liquid chromatography (normal value <6.2%), C-peptide level by electrochemiluminescence, and capillary pH. Diabetic ketoacidosis (DKA) was defined according to the ISPAD criteria [7]. The β-hydroxybutyrate level was measured by capillary method. Diabetes-associated autoantibodies were measured before insulin administration and determined by liquid-phase radiobinding assays. SARS-CoV-2 positivity was assessed by polymerase chain reaction (PCR) test from a nasopharyngeal swab at admission.

SARS-CoV-2 serology was collected during the first month of diabetes and total antibodies (IgG, IgM, and IgA) were measured by Elecsys® Anti-SARS-CoV-2 from Roche on Cobas 801. A second sample was taken 3–12 weeks after the first sampling. The study was approved by the medical ethical committee of the hospital and conducted in accordance with the protocols used by our institution. Many variables were not normally distributed, so results are presented as median (interquartile range). Comparisons were performed using the Wilcoxon rank-sum test, X^2 test, or Fisher's exact test. Two-tailed statistical tests were performed using SPSS version 27. A p-value <0.05 was considered statistically significant.

Our children's hospital accepts children aged 0–16 years. Between 1 March 2020 and 28 February 2021, 86 patients were diagnosed with type 1 diabetes (see Figure 1). Of the 75 who accepted to participate, only one (1%) was SARS-CoV-2 PCR positive. We found anti-SARS-CoV-2 antibodies positivity in 15 (20%) patients. Participants with positive anti-SARS-CoV-2 antibodies had an increased bicarbonate and base excess compared to participants without anti-SARS-CoV-2 antibodies (Table 1). There were no differences in sex, age, pH, HbA_{1c}, or glycemia. Overall 22 (29%) patients presented DKA at diagnosis and 2 (9%) of them were positive for anti-SARS-CoV-2 antibodies. Of the 75 participants, 54 (72%) were insulinoma-associated protein 2 antibodies (IA2A) positive but IA2A positivity had significantly higher frequencies in children without anti-SARS-CoV-2 antibodies (49 (81%) vs. 5 (33%), p=0.038). Nine (15%) patients, initially seronegative, have developed anti-SARS-CoV-2 antibodies between the two samples (mean time 8 ± 4 weeks).

This study provides the prevalence of anti-SARS-CoV-2 antibodies among Belgian children with new-onset type 1 diabetes during the first year of the SARS-CoV-2 pandemic. Sciensano reported that 12.4% of children had anti-SARS-CoV-2 antibodies [8]. This study also showed regional differences in the prevalence of antibodies: it is highest in the Brussels region (24%). As in another study [9], our results in the specific population of children with newly diagnosed type 1 diabetes are quite similar to that of the general population.

A bi-directional link between SARS-CoV-2 and diabetes has been described: people with diabetes are more exposed to severe SARS-CoV-2 and SARS-CoV-2 has been associated with the onset of type 1 diabetes [10, 11] but this association remains controversial. Angiotensin-converting enzyme 2 has been identified as a receptor for the peak protein of the SARS-CoV-2 [12]. This enzyme is expressed on pancreatic beta cells, so SARS-CoV-2 could induce their destruction, leading to diabetes. But younger children have lower expressions of angiotensin-converting enzyme 2 compared to older children and adults [13]. With this in mind, we could hypothesize that during the pandemic, more adolescents and young adults could develop diabetes. In our study, the average number of new diagnoses of type 1 diabetes in our center over the last 3 years is 67, which is slightly lower than the number of new cases observed during the pandemic (pNS). But, we could not identify more type 1 diabetes in adolescents during this pandemic compared to the previous three years (proportion of children aged 12–16 during the pandemic 68 vs. 69% the previous three years; pNS).

In our study, the frequency of diabetes-associated autoantibodies was similar in patients with and without anti-SARS-CoV-2 antibodies, except for IA2A, less frequent in the presence of anti-SARS-CoV-2 antibodies. The underlying mechanism of diabetes may be different in SARS-CoV-2 infection. Indeed, a recent case report described how the SARS-CoV-2 infection could be a possible cause for type 1 diabetes onset in subjects presenting with diabetes-associated autoantibodies negative DKA [14]. They suggest that, in adults, SARS-CoV-2 can adhere to human islet cells,

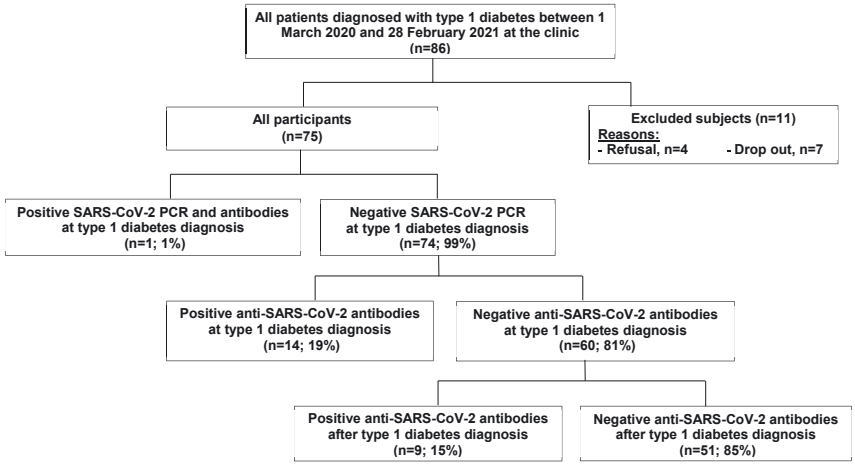

Figure 1: Patient enrollment flow chart.

Table 1: Characteristics of the study population at type 1 diabetes diagnosis.

	All subjects n=75	Positive SARS-CoV-2 antibodies n=15	Negative SARS-CoV-2 antibodies n=60	p-Value
Male, n, %	47 (63)	8 (57)	39 (64)	0.761
Age at diagnosis, yrs	10.1 (6.8–12.6)	10.5 (3.3–13.6)	9.9 (6.8–12.6)	0.957
pH	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.4 (7.2–7.4)	0.098
HbA_{1c}, %	11.7 (9.9–12.8)	10.6 (9.4–12.8)	11.8 (10.1–12.8)	0.431
C peptide, nmol/L	0.208 (0.124–0.381)	0.229 (0.119–0.343)	0.208 (0.124–0.399)	0.687
B-hydroxybutyrate, mmol/L	4.1 (0.7–6.1)	3.9 (0.5–5.2)	4.1 (1.2–6.2)	0.298
Glycemia, mg/dL	422 (311–574)	413 (296–667)	430 (314–570)	0.543
Glycemia, mmol/L	23.4 (17.3–31.9)	22.9 (16.4–37.0)	23.9 (17.4–31.6)	0.543
Base excess, mEq/L	−4.5 (−14.8–1.2)	1.1 (−6.1–2.8)	−5.4 (−16.7–0.3)	**0.033**
Bicarbonate, mmol/L	21.0 (12.0–26.0)	23.5 (18.8–28.0)	20.1 (10.0–25.0)	**0.043**
GADA positivity, n, %	47 (63)	9 (62)	38 (63)	0.913
IAA positivity, n, %	36 (48)	6 (43)	29 (49)	0.771
IA2A positivity, n, %	54 (72)	5 (33)	49 (81)	**0.038**
PCR SARS-CoV-2 positivity, n, %	1 (1)	1	0	0.187

GADA, glutamic acid decarboxylase antibodies; IAA, insulin autoantibodies; IA2A, insulinoma-associated protein 2 antibodies; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. All value are shown as median (IQR) excluding gender, auto antibodies and PCR positivity as n (%). Comparisons between groups were performed using one-way ANOVA, X^2 test or Fisher's exact test depending on the subgroup size. A p-value <0.05 was considered statistically significant.

infect islet cells and then cause potentially virus-mediated toxicity or autoimmunity against the virus within the pancreas. But the temporal relationship between SARS-CoV-2 infection and the development of diabetes remains to be elucidated, especially in children.

During follow-up, 15% of our patients developed anti-SARS-CoV-2 antibodies. It should be noted that in Belgium, the SARS-CoV-2 epidemic experienced a second wave of infections end of October 2020 [15]. This seroconversion therefore may reflect the evolution of the epidemic in the Belgian population.

This observation is the first to report the prevalence of anti-SARS-CoV-2 antibodies in a pediatric population with new-onset type 1 diabetes in Belgium. The observational design allowed us to include almost all new patients in our center but did not allow us to establish causal links. Our data also come from a single academic center, and may therefore not be fully representative of other populations.

In conclusion, this study showed a prevalence of anti-SARS-CoV-2 antibodies in children with newly diagnosed type 1 diabetes similar to that observed in children without diabetes in a country severely affected by this pandemic. Longer-term follow-up is needed to define a possible link between the SARS-CoV-2 pandemic and the development of autoimmune diabetes in children.

Research funding: None declared.

Author contributions: AM designed the study, collected the data, undertook the analysis, interpreted results, wrote the manuscript, reviewed and edited the manuscript, and takes full responsibility for the integrity of data and the accuracy of data analysis. ST and LH collected the data and reviewed the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

References

1. Atkinson M, Eisenbarth G, Michels A. Type 1 diabetes. Lancet 2014; 383:69–82.
2. Krolewski A, Warram J, Rand L, Khan C. Epidemiologic approach to the etiology of type 1 diabetes mellitus and impaired glucose tolerance in adults. N Engl J Med 1987;317:1390–8.
3. Moore M. Enteroviral disease in the United States, 1970–1979. J Infect Dis 1982;146:103–8.
4. Ruiz P, Tapia G, Bakken I, Haberg S, Hungnes O, Gulseth H, et al. Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. Diabetologia 2018;61:1996–2004.
5. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382: 1708–20.
6. Rubino F, Amiel S, Zimmet P, Alberti G, Bornstein S, Eckel R, et al. New-onset diabetes in COVID-19. N Engl J Med 2020;383:789–90.
7. Mayer-Davis E, Kahkoska A, Jefferies C, Dabelea D, Balde N, Gong C, et al. ISPAD clinical practice consensus guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2018;19:7–19.

8. Duysburgh E, Merckx J, Callies M, Kabouche I, Roelants M, Vermeulen M, et al. Prevalence and incidence of antibodies against SARS-CoV-2 in children and school staff measured between December 2020 and June 2021: an observational seroprevalence prospective cohort study – findings of the first testing period. Brussels, Belgium: Sciensano; 2021. Report number: D/2021/14.440/10.
9. Jia X, Gesualdo P, Geno Rasmussen C, Alkanani A, He L, Dong F, et al. Prevalence of SARS-CoV-2 antibodies in children and adults with type 1 diabetes. Diabetes Technol Therapeut 2021; 25. https://doi.org/10.1089/dia.2020.0609 [Online ahead of print].
10. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020;8:813–22.
11. Unsworth R, Wallace S, Oliver N, Yeung S, Kshirsagar A, Naidu H, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020;43: e170–1.
12. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.
13. Mohaghegh S, Motie P, Motamedian S. Role of ACE2 polymorphism in COVID-19: impact of age. Clin Chem Lab Med 2021. https://doi.org/10.1515/cclm-2020-1877 [Online ahead of print].
14. Venkatesh N, Astbury N, Thomas MC, Rosado CJ, Pappas E, Krishnamurthy B, et al. SARS-CoV-2 as a potential cause of type 1 diabetes facilitated by spike protein receptor binding domain attachment to human islet cells: an illustrative case study and experimental data. Diabet Med 2021: e14608. https://doi.org/10.1111/dme.14608 [Epub ahead of print].
15. Cornelissen L, Litzroth A, Montourcy M, De Rouck M, Wyndham-Thomas C, Klamer S, et al. Rapport thématique infection COVID-19 chez les enfants en Belgique : Résultats de la surveillance laboratoire, données scolaires et surveillance clinique des patients hospitalisés jusqu'au 28 juin. Bruxelles, Belgique: Sciensano; 2020. Numéro de dépôt : D/2020/14.440/69.