Analysis of pancreatic function in pediatric patients with COVID-19

Análisis de la función pancreática en pacientes pediátricos con COVID-19

Dear Editor:

There has been a striking increase in the number of newly diagnosed cases of type 1 diabetes in children in the context of the coronavirus disease 2019 (COVID-19) pandemic.[1,2]

With the aim of assessing short-term pancreatic function in children with mild infection by SARS-CoV-2, we conducted a multicentre prospective study in 4 Spanish hospitals between September 2020 and June 2021. The study included 89 patients with a diagnosis of SARS-CoV-2 infection by RT-PCR or antigen testing of nasopharyngeal samples. Thirty days after the diagnosis, having obtained informed consent, we collected a fasting venous blood sample for the following tests: lipid profile, complete blood count and chemistry panel, basal insulin and C-peptide levels (chemiluminescence immunoassay) and concentration of glycated haemoglobin (HbA_{1c}) (ion-exchange reverse-phase high performance liquid chromatography; normal range, 4%–5.7%).

The mean duration of symptoms at the time of diagnosis was 1.8 days (standard deviation [SD], 1.8). The most frequent manifestations were respiratory symptoms (51.7%) and fever (48.3%) (Table 1). Only one patient was hospitalised due to suspicion of paediatric inflammatory multisystem syndrome.

Table 1 Characteristics of the patients.

	n (%)
Sex distribution	
Male	46 (51.7%)
Female	43 (48.3%)
Age distribution (years)	
<1	7 (7.9%)
1-3	9 (10.1%)
3-6	12 (13.5%)
6-12	33 (37.1%)
>12	28 (31.5%)
Ethnicity	
European/Caucasian	78 (87.6%)
Latin American	8 (9%)
Arab	3 (3.4%)
Family history of diabetes	
Type 1	3 (3.4%)
Type 2	37 (41.6%)
Characteristics of SARS-CoV-2 infection	
Fever	43 (48.3%)
Respiratory symptoms	46 (51.7%)
Gastrointestinal symptoms	20 (22.5%)
Changes in taste/smell	4 (4.5%)
PIMS	1 (1.1%)

PIMS, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

The mean concentration of HbA_{1c} was 5.2% (significantly lower in female patients: 5.1% versus 5.3%; $P = 0.006$) with a statistically significant correlation between age and the HbA_{1c} concentration (Pearson r, 0.452; $P < 0.001$). None of the patients had HbA_{1c} levels of 6.5% or greater (range, 4.3%–5.9%); however, 5 patients (5.5%) had values of 5.7% or greater (80% with a body mass index [IMC] above the 90th percentile).

The mean level of C-peptide was 1.3 ng/mL (SD, 0.7), with no differences based on sex ($P = 0.289$). Thirty-seven percent of patients had levels of less than 1 ng/dL; in this subset, the mean HbA_{1c} concentration was 5%. We found a statistically significant correlation between age and C-peptide levels (Pearson r, 0.456; $P < 0.001$).

The mean blood insulin level was 8.5 μU/mL (SD, 6), without differences based on sex ($P = 0.289$). We found a weak correlation between blood insulin levels and age (Pearson r, 0.392; $P < 0.001$) and a moderate correlation between insulin levels and BMI (Pearson r, 0.477; $P < 0.001$).

The mean fasting blood glucose level was 88.2 mg/dL (SD, 10.2). None of the patients met the criteria for diabetes. In 6 patients (6.6%), we found abnormal fasting glucose levels (values ranging from 100 to 125 mg/dL); 3 of these patients (50%) had a BMI above the 97th percentile, although none had dyslipidaemia and all had HbA_{1c} concentrations below 5.7% (Fig. 1).

Based on our current knowledge on the pathophysiology of COVID-19, some authors have attributed a direct role in the development of type 1 diabetes to SARS-CoV-2.[3] The virus uses the angiotensin converting enzyme 2 receptor to enter and infect host cells, and this receptor is expressed both in the lung and in the endocrine pancreas. There is ample documentation of the pancreatic damage caused by SARS-CoV-2 in adults, but when it comes to the paediatric population, this issue remains to be elucidated.

A recently published study by the Centers for Disease Control and Prevention of the United States analysed the risk of newly diagnosed diabetes (type 1, 2 or other) more than 30 days after the diagnosis of acute SARS-CoV-2 infection in patients aged less than 18 years,[4] and found a significantly greater incidence of diabetes in patients with COVID-19. However, as the authors themselves noted, a percentage of these new cases of diabetes probably occurred in patients with prediabetes, a condition that is present in 1 out of 5 adolescents in the United States.[5]

Our findings suggest that the hypothetical pancreatic damage induced by SARS-CoV-2 would be transient and mild. None of the patients had HbA_{1c} or fasting glucose levels meeting the criteria for diagnosis of diabetes, and while 5 patients had HbA_{1c} concentrations of 5.7% or greater and 6 patients fasting glucose levels in the abnormal range, this was more likely related to their BMI rather than the infection by SARS-CoV-2.

Although the study was conducted in several centres, the sample was small and could not be considered representative of the general population of paediatric patients affected by COVID-19. Since similar studies have not been published before, we were unable to compare our findings with those of other researchers. We also do not know whether the cases in our sample were caused by the same variant of the virus or different variants. This could be relevant, since, as has occurred with other RNA retroviruses, as

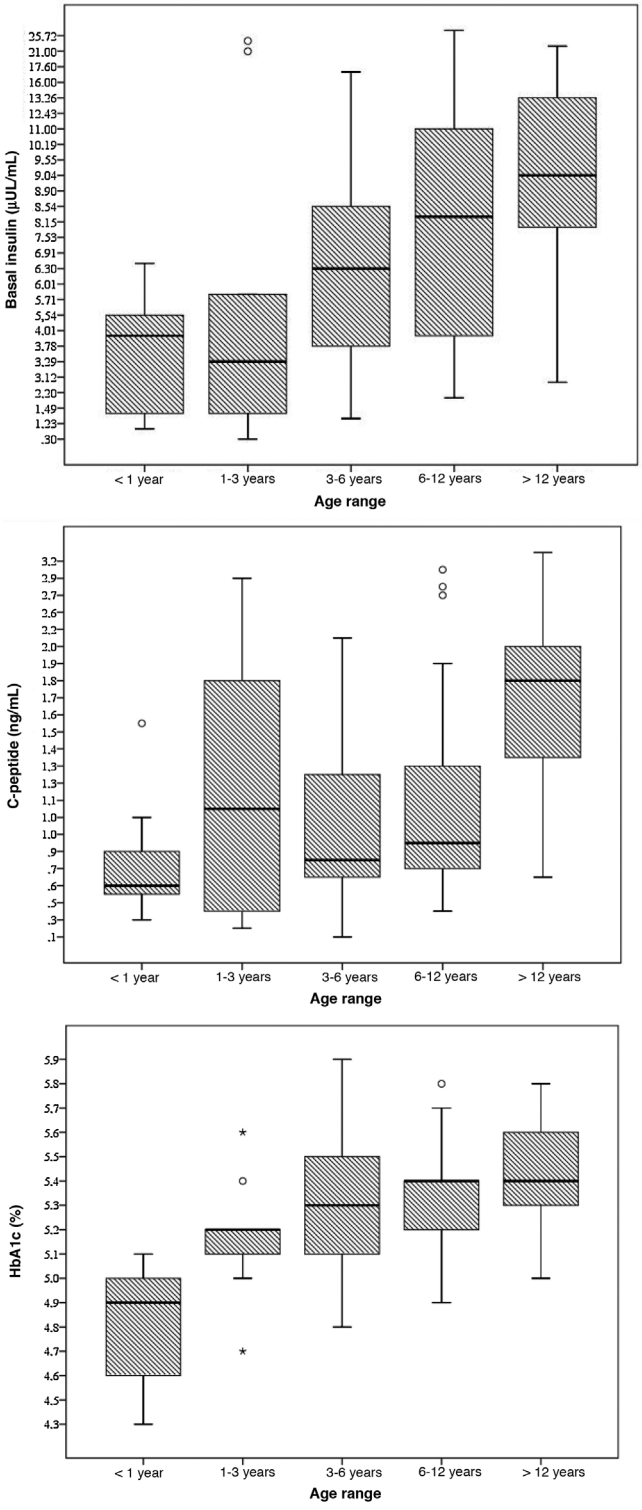

Figure 1 Analysis of pancreatic function.

the pandemic has evolved, so has the genome of the virus and, consequently, its intrinsic characteristics related to its transmissibility or virulence.[6]

In conclusion, in this case series we did not find evidence of SARS-CoV-2 infection in children causing significant changes in pancreatic function or glucose metabolism, at least in the short term. Our results should be confirmed in larger population-based studies.

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Appendix A. Research Group on Urgent Paediatric Endocrinological Diseases

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Treatment for acquired aplasia and refractory cytopenia. Review of a historical cohort☆

Tratamiento de la aplasia adquirida y la citopenia refractaria. Revisión de una cohorte histórica

Dear Editor:

Recently, we reviewed the experience in our hospital in the management of acquired aplastic anaemia (AAA) and refractory cytopenia in childhood (RCC), in accordance with the recommendations and studies associated with the a European Society for Blood and Marrow Transplantation (EBMT).[1,2] Acquired aplastic anaemia is the most common form of acquired bone marrow failure, with an estimated incidence of 1.5 cases per 2 million individuals per year in Europe.[1] Refractory cytopenia in childhood is the most common myelodysplastic syndrome in children. It is recommended that these patients receive the same treatment established for AAA, based on haematopoietic stem cell transplantation (HSCT) or immunosuppressive therapy (IST).[3] The aim of our study was to retrospectively assess the response rate, event-free survival and overall survival of patients with AAA and RCC that underwent HCST or IST.

The study included 48 patients with a diagnosis of AAA or RCC managed at the Hospital Infantil Universitario Niño Jesús between 2001 and 2020. Two patients (4.08%) did not received treatment, one due to spontaneous recovery and the other due to paroxysmal nocturnal haemoglobinuria (PNH) clone expansion, which did not require treatment until the patient was transferred to another centre. We defined complete remission (CR) as a neutrophil count of 1.5×10^9/L or greater, a platelet count of 150×10^9/L or greater and a haemoglobin concentration of 10.5–13 g/dL.[1] We defined partial remission (PR) as the achievement of transfusion independence. The events taken into account

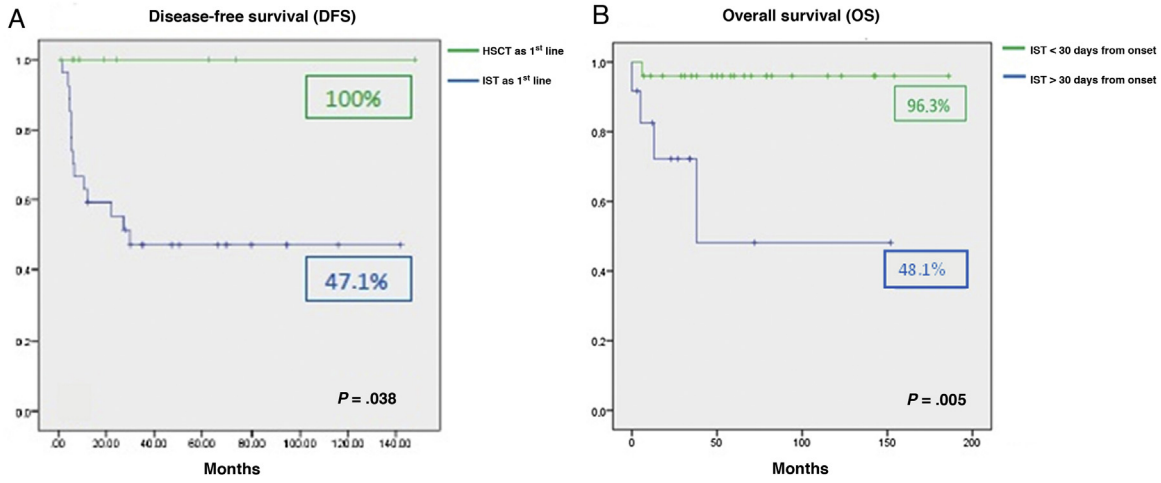

Figure 1 (A) Disease-free survival in the cohort following first-line treatment. (B) Overall survival after immunosuppressive therapy depending on the time elapsed from diagnosis to treatment.

☆ Previous presentations: This study was presented in the LXIII National Congress of the Sociedad Española de Hematología y Hemoterapia and the XXXVII National Congress of the Sociedad Española de Trombosis y Hemostasia, held in 2021 in Pamplona, Spain.