Short Communication

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Role of the SARS-CoV-2 virus in the appearance of new onset type 1 diabetes mellitus in children in Gran Canaria, Spain

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Abstract

Objectives: It has been hypothesized that SARS-CoV-2 may play a role in the development of different forms of diabetes mellitus (DM). The Canary Islands have the highest incidence of type 1 DM (T1DM) reported in Spain (30–35/100,000 children under 14 years/year). In 2020–2021 we observed the highest incidence so far on the island of Gran Canaria, as a result of which we decided to evaluate the possible role of COVID-19 in the increased number of onsets.

Methods: We examined the presence of IgG antibodies against SARS-CoV-2 in children with new onset T1DM between October 2020 and August 2021. We compared recent T1DM incidence with that of the previous 10 years.

Results: Forty-two patients were diagnosed with T1DM (48.1/100,000 patients/year), representing a nonsignificant 25.7% increase from the expected incidence. Of the 33 patients who consented to the study, 32 presented negative IgG values, with only one patient reflecting undiagnosed past infection. Forty-four percent of patients presented with ketoacidosis at onset, which was similar to previous years.

Conclusions: We conclude that there is no direct relationship between the increased incidence of T1DM and SARS-CoV-2 in the region. The COVID-19 pandemic did not result in an increased severity of T1DM presentation.

Keywords: children; COVID-19; incidence; type 1 diabetes.

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Following the onset of the COVID-19 pandemic, some authors reported an increase in the number patients presenting with new onset type 1 diabetes mellitus (T1DM) [1], as well as an increase in the proportion of children presenting with diabetic ketoacidosis (DKA), although these findings are not generalized [2, 3].

Some authors have also reported cases of patients with active or recent SARS-CoV-2 infection and new diabetes onset in the absence of pancreatic autoimmunity. Angiotensin converting enzyme type 2 (ACE2), the cellular

receptor used by the virus to infect humans, is expressed in the pancreas, and other coronaviruses show both affinity for the β-cell and diabetogenic potential. This has led experts in the field to evaluate the pathogenesis of COVID-19-related diabetes in order to consider possible differences to other known forms of diabetes [4] (covidiab.e-dendrite.com [5]).

The Canary Islands are the southernmost region of Spain, located 100 km off the coast of Morocco. With a genetic background influenced by European, northern African and, to a lesser extent, sub-Saharan populations [6], it is the region with the highest reported T1DM incidence in Spain [7].

Seven months after the onset of the pandemic, we began to observe an increase in the number of new onset cases compared to previous years. Given the existing reports describing a possible role of the SARS-CoV-2 virus in the onset of T1DM, we evaluated the influence of the virus on the apparent increase in the number of cases in the Canarian pediatric population.

In September 2021 we performed a retrospective evaluation of all children under 14 years of age who were diagnosed with T1DM between October 1, 2020 and August 31, 2021. T1DM was diagnosed following ADA criteria [8]. Reverse-transcription polymerase chain reaction (Rt-PCR) was performed in all patients at the time of onset. Detection of immunoglobulin G (IgG) antibodies against COVID-19 nucleocapsid and spike proteins was performed using two microparticle chemiluminescence (CMIA) techniques. An anti-nucleocapsid antibody index greater than or equal to 1.4 (Alinity, Abbott Diagnostics), as well as an anti-spike value greater than 50 AU/mL, was considered positive.

Eleven-month incidence was computed by dividing the number of cases (October–August) by the total population for the age group and adjusting for 100,000 children less than 14 years of age at risk. Yearly incidence was computed by extrapolating the 11-month data. Incidence for the 10-year period was computed by dividing the total number of cases by the total number of children at risk for the whole period and adjusting for 100,000 children. Age-standardized rates were computed by the direct method and using the standard European population distribution published by the WHO. Ninety five percent confidence intervals (CI) were calculated for all incidence rates. Proportion of first-degree relatives with T1DM was described for the last five years. Temporal trend analysis was performed using Poisson regression. The R V4.1.1 computing environment (R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis.

We also evaluated the presence of DKA at onset, known past COVID-19 infection, and the vaccination status of all patients. To the best of our knowledge, all patients presenting with new onset T1DM in Gran Canaria during the study period were referred to our clinic.

Anti-islet autoantibodies were measured at onset in our patients using radioimmunoassay (RIA) by Reference Laboratory S.A. (Barcelona, Spain). The islet antigen 2 (IA2) autoantibody RIA kit from RSR (Ldt, Cardiff, UK) with 125I-labeled IA2 was used for the detection of IA2 antibodies. The glutamic acid decarboxylase (GAD) autoantibody RIA kit from RSR with 125I-labeled GAD was used for the detection of GAD antibodies. The DIAsource AIA-100 kit was used for the detection of anti-insulin antibodies.

A total of 42 patients presented with T1DM between October 1, 2020 and August 31, 2021. Table 1 summarizes the number of patients, providing crude and adjusted incidence rates for the last 10 years. There is a significant linear increase in incidence of 4.9% per year over the last 10 years (95% CI: 0.9–9; p=0.016). However, this trend is attenuated and loses statistical significance if we do not take into account the 2020–21 period (2.2% increase 95% CI: −2.5 to 7.1; p=0.36). In an effort to evaluate whether this year's increase in incidence was unusual, we computed the expected incidence of the 2020–21 period using the data from the previous years. The expected incidence for 2020–21 was 38.3/100,000, meaning that the obtained incidence (48.1/100,000) is 25.7% higher than expected (Figure 1), although the difference (9.8%; 95% CI: −8.3 to 28%) was not statistically significant (p=0.29). We did not find any differences in age distribution at onset during the study period (Table 1). Forty-four percent of our patients presented with DKA at onset compared to an average of 40% during the previous three years (Table 1).

All patients presented a negative Rt-PCR at the time of onset. One of our patients and his parents were diagnosed with COVID-19 in September 2020, confirmed by positive Rt-PCR. All other patients were offered serological testing. Thirty-three of the 41 new-onset patients who were not diagnosed with COVID-19 consented to the serological study. Only one had positive IgG anti-nucleocapsid titers. Four patients who had received two doses of the mRNA-1273 vaccine (ModernaTX Inc, Cambridge, Massachusetts, US), presented positive IgG anti-spike antibody titers but negative anti-nucleocapsid antibodies (reflecting response to the vaccine but not past SARS-CoV-2 infection).

Regarding autoimmunity, anti-islet autoantibodies were measured at onset in most of our patients. Of the 42 patients, 40 were positive for at least one antibody (95% of our sample), one was negative for all three antibodies, and one did not undergo the test.

We report an incidence of T1DM in Gran Canaria of 48.1/100,000 (see Figure 1), which is the highest reported

Table 1: Crude and adjusted yearly incidence. Cases with DKA.

	2011–12	2012–13	2013–14	2014–15	2015–16	2016–17	2017–18	2018–19	2019–20	2020–21	Total
Number of new cases	33	34	20	26	28	30	29	32	28	42	302
Population <14 years	117,699	116,063	113,304	110,477	107,669	105,035	102,954	100,405	97,791	95,204	1,066,601
% cases per age group											
0–4	30.3%	17.6%	40%	7.7%	17.8%	16.7%	17.2%	28.1%	32.1%	26.2%	23.2%
5–9	33.3%	35.3%	30%	57.7%	35.7%	53.3%	41.4%	25%	32.1%	33.3%	37.4%
10–13	36.4%	47.1%	30%	34.6%	46.4%	30%	41.4%	46.9%	35.7%	40.5%	39.4%
Crude incidence[a] (95% CI)	30.6 (21.06–44)	32 (21.8–45.1)	19.3 (11.4–29.6)	25.7 (16.9–38)	28.4 (18.6–40.4)	31.2 (21–44)	30.7 (21–44)	34.8 (24.3–48.6)	31.2 (21–44)	48.1 (35.3–63.6)	30.9 (21–44)
Adjusted incidence[a] (95% CI)	30.4 (20.2–42.8)	30.3 (20.2–42.8)	20.1 (12.2–30.8)	23.3 (14.5–34.5)	26.7 (17.7–39.2)	29.7 (20.2–42.8)	28.9 (19.4–41.6)	33.9 (23.5–47.5)	31.6 (21.8–45.1)	47.1 (34.5–62.5)	29.9 (20.2–42.8)
Incidence per age group[a]											
0–4	28.92	18.19	25.77	6.69	17.36	17.89	18.25	33.28	34.66	43.28	24.05
5–9	27.03	29.70	15.12	39.14	26.89	44.84	34.66	24.03	27.58	44.05	31.02
10–13	36.80	48.48	18.11	27.24	39.73	27.56	37.08	47.31	32.22	56.54	36.92
Ketoacidosis at onset							45%	32%	42%	44%	
Proportion of positive T1DM family history[b]					2 (7.1%)	2 (6.6%)	3 (10.3%)	5 (15.6%)	5 (17.8%)	3 (7.1%)	

[a]Cases/100,000/year children <14 years of age; [b]history of T1DM in first degree relatives of patients diagnosed with T1DM.

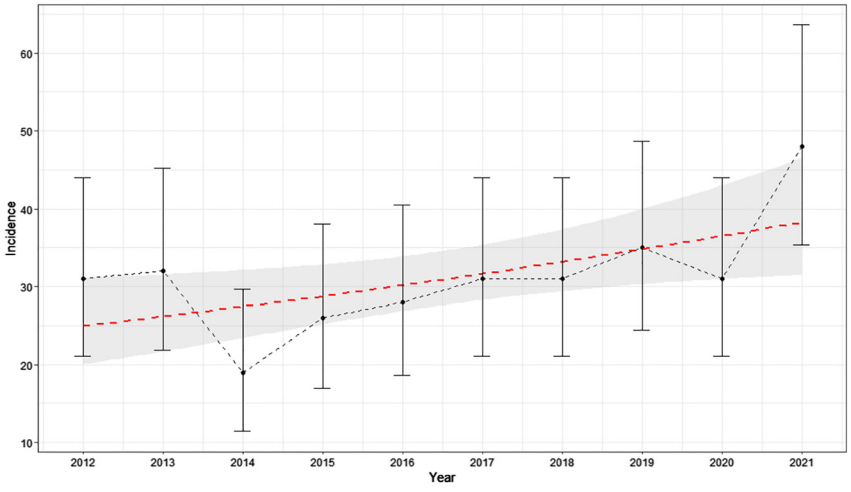

Figure 1: Yearly incidence and expected incidence for Oct-21/Aug-22.
Yearly incidence and 95% CI are reported for each period from 2012 to 2021. Predicted incidence for the 2020–21 period is drawn in yellow.

since registration of cases began in 2006 [7]. The reported incidence is 25.7% higher than expected, although the difference is statistically non-significant. Serological studies did not support a direct association between SARS-CoV-2 infection and T1DM onset. However, data from other coronaviruses suggests a decline in antibody titers after one year [9], limiting our capacity to evaluate possible SARS-CoV-2 infections prior to September 2020.

The relationship between respiratory infections and the development of pancreatic autoantibodies has been established in children at genetic risk by the TEDDY study [10]. Establishing a direct link between SARS-CoV-2 infection and new onset T1DM is not easy. Two strengths of our study are measurement of SARS-CoV-2 antibodies, which is not common in similar studies, and the fact that we are the pediatric diabetes reference center for Gran Canaria. We

also acknowledge some limitations: the relatively small sample size, the time of antibody measurement, and the study period itself, which started seven months after the onset of the pandemic.

In our sample, 95% of patients presented positive islet-cell autoimmunity, strongly suggesting that they have typical T1DM rather than other types of DM potentially associated with SARS-CoV-2 [4]. The role that SARS-CoV-2 may play in the appearance of new T1DM cases, or indeed whether it is relevant at all, is not clear. After some case reports and a meta-analysis in which up to 14% of patients (mainly adults) infected with SARS-CoV-2 presented with new onset diabetes [11], and early studies reporting increased incidence of T1DM following the beginning of the pandemic, greater attention has been given to the possible role of SARS-CoV-2 in the pathogenesis of the disease. The question of whether it accelerates an ongoing autoimmune process, serves as a trigger, or causes direct damage through interaction with ACE2 receptors in the pancreas [4] remains unanswered.

Unsworth et al. [1] reported an increase in the number of incident cases in some regions of the UK between March and June 2020, along with positive serological reports in some cases and an increased number of patients presenting with DKA, suggesting a possible relationship between SARS-CoV-2 infection and new onset T1DM. More recently, Vlad et al. reported an increase in the number of incident cases of T1DM in Romania during 2020 [12], although present or past SARS-CoV-2 infection was not evaluated. It is important to point out that substantial interannual variability in incident cases has been reported in multiple studies previous to the appearance of COVID-19 [7, 13]. Increased incidence without evidence of SARS-CoV-2 infection does not support a role of COVID-19 in DM pathogenesis.

Other authors have not reported an increased number of onsets after the beginning of the SARS-CoV-2 pandemic, and advocate for a coordinated effort in the evaluation of questions relating to the effect of COVID-19 in the onset of diabetes [14]. Tittel et al. evaluated the number of new cases at 217 German DPV-registered centers between March and May 2020, and compared it to the same period since 2011. They did not report an increase in incidence. In Colorado (USA), Xiaofan et al. reported similar infection rates in children with new onsets compared to established T1DM and healthy individuals between January and October 2020 [3]. Recently, Messaaoui et al. also failed to find evidence of a relationship between SARS-CoV-2 and new onset T1DM in children [15].

To conclude, we found a higher-than-expected, although not statistically significant, number of patients presenting with new onset T1DM in an 11-month period starting seven months after the first case was reported on Gran Canaria. However, the lack of serological evidence suggesting a direct relationship between the virus and the new cases leads us to conclude that there is no direct relationship between the increased incidence and SARS-CoV-2 in the region.

International coordinated initiatives like the Covidiab registry [4] are needed in order to gain a deeper understanding of the role SARS-CoV-2 plays in the pathogenesis of T1DM.

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