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Association between COVID-19 and the incidence of type 1 diabetes in Portugal – a registry study

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Abstract

Background Viral respiratory infections may precipitate type 1 diabetes (T1D). A possible association between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, and the incidence of T1D is being determined. This study was carried out using Portuguese registries, aiming at examining temporal trends between COVID-19 and T1D.

Methods Hospital data, comparing the incidence before and during the COVID-19 pandemic, from children and young adults diagnosed with new-onset T1D, was acquired beginning in 2017 and until the end of 2022. Data was obtained from nine different Portuguese hospital units. The impact of the COVID-19 pandemic, beginning in March 2020, was assessed comparing the annual numbers of new-onset T1D cases. The annual median levels of glucose, glycated hemoglobin (HbA1c) and fasting C-peptide at T1D diagnosis were compared. The annual number of diabetic ketoacidosis (DKA) episodes among new T1D cases was also assessed at two centers.

Results In total, data from 574 newly diagnosed T1D patients was analyzed, including 530 (92.3%) children. The mean ages for child and adult patients were 9.1 (SD 4.4) and 32.8 (SD 13.6) years, respectively. 57.8% (331/573) were male, one patient had unknown sex. The overall median (25–75 percentiles) levels of glucose, HbA1c and fasting C-peptide at diagnosis were 454 mg/dL (356–568), 11.8% (10.1–13.4) and 0.50 µg/L (0.30–0.79), respectively. DKA at T1D diagnosis was present in 48.4% (76/157). For eight centers with complete 2018 to 2021 data (all calendar months), no overall significant increase in T1D cases was observed during the COVID-19 pandemic, i.e. 90 cases in 2018, 90 cases in 2019, 112 in 2020 and 100 in 2021 (P for trend = 0.36). Two of the centers, Faro (CHUA) and Dona Estefânia (CHULC) hospitals, did however see an increase in T1D from 2019 to 2020. No significant changes in glucose ($P=0.32$), HbA1c

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($P=0.68$), fasting C-peptide ($P=0.20$) or DKA frequency ($P=0.68$) at the time of T1D diagnosis were observed over the entire study period.

Conclusion The T1D incidence did not increase significantly, when comparing the years before and during the COVID-19 pandemic, nor did key metabolic parameters or number of DKA episodes change.

Keywords Type 1 diabetes, COVID-19, Portugal

Background

Type 1 diabetes (T1D) belongs to the group of autoimmune diseases and is characterized by gradual destruction of the pancreatic β -cells, resulting in insulin deficiency. Although the clinical manifestations of T1D are well characterized, with autoimmune biomarkers found in 70–90% of the patients [1], the exact pathogenesis remains elusive. It has been hypothesized that certain viral infections, including those caused by enterovirus, are involved and can induce T1D [2, 3]. The proposed mechanisms include both direct pancreatic damage and the precipitation of autoimmune development [4]. In Northern Europe, the T1D incidence is usually highest during the winter, where respiratory viral infections are also most common, providing further support for the virus induced T1D theory [5, 6].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus linked to the coronavirus disease 2019 (COVID-19), which became a pandemic during March 2020, affecting virtually all countries [7]. Though COVID-19 symptoms are predominantly respiratory, the SARS-CoV-2 can infect many parts of the body, through binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is also densely distributed in the pancreas [8, 9]. Early during the COVID-19 pandemic it was hypothesized that the SARS-CoV-2 could induce T1D. Thus, a marked increase in T1D cases was found at a pediatric center in the United Kingdom from March to June 2020 [10]. Since then, a number of mainly register based studies have investigated this association and the results have been conflicting. A large investigation from the United States, based on the medical insurance claims databases, found a higher incidence of diabetes among young patients <18 years after SARS-CoV-2 infection [11], while a study from Scotland with detailed information on the date of T1D diagnosis and SARS-CoV-2 PCR testing did not replicate this finding [12]. A meta-analysis including 26 papers reported an increase in T1D [13], as did another recently published systematic review of 42 studies with meta-analysis [14], though data from the worldwide SWEET register did not find evidence of a link between COVID-19 and T1D [15]. A large Canadian cohort study recently reported an increase in the diabetes frequency following the COVID-19 pandemic, but it could not establish a correlation specifically for T1D, possibly due to the low T1D numbers

[16]. In Denmark, no association was observed in a prospective register investigation among children and young adults [17], and another Danish register study evaluating the entire population below 30 years similarly reported no association [18].

In the present multicenter study, we report incidence data on new-onset T1D cases across Portugal before and during the COVID-19 epidemic to determine its impact on T1D development. We further provide an analysis on the changes in glycemic levels and endogenous insulin production at T1D diagnosis, before and during the epidemic. Finally, we evaluate the annual number of diabetes ketoacidosis (DKA) episodes, as well as previous COVID-19 infection as a risk factor for DKA at the time of T1D diagnosis.

Methods

Data collection

The study was a retrospective and hospital-based evaluation comprising new-onset T1D cases and COVID-19 related data from nine hospital units across Portugal, from January 2017 to December 2022. Complete data for all calendar months were, however, only available from eight centers from 2018 to 2021.

Most sites were pediatric centers, including the hospitals Santa Maria and Dona Estefânia in Lisbon, Centro Hospitalar in Leiria, Hospital Santa Maria Maior in Barcelos, Hospital Espírito Santo in Évora, Centro Hospitalar Universitário do Algarve in Faro, the Pediatric Hospital in Coimbra, and the pediatric unit at Centro Hospitalar de Vila Nova de Gaia/Espinho. Only one adult center, Hospital de Portimão e Lagos at the Algarve Coast, participated.

The Centro Hospitalar de Vila Nova de Gaia/Espinho did not have complete data available from the last part of 2021 and was therefore not included in the T1D case trend analysis. It was, however, included in the analysis of the metabolic parameters.

Data variables

The demographic and clinical information of new-onset T1D cases included age, gender, symptoms at diabetes diagnosis, height, weight, blood pressure, family history of T1D (any relative), other illnesses and COVID-19 infection (usually PCR or Quick-test confirmed) prior to or concurrent with T1D diagnosis.

The Bacillus Calmette-Guérin (BCG) vaccine has previously been suggested as a possible protective factor in terms of COVID-19 severity [19], and we therefore recorded previous BCG vaccination. For one center, data could also be extracted on prior COVID-19 vaccination.

Biochemical data included initial random glucose and glycated hemoglobin (HbA1c) at first presentation (time of diagnosis), fasting C-peptide (as a measure of endogenous insulin production), low density lipoprotein (LDL), total cholesterol and the presence of anti-glutamic acid decarboxylase (GAD) and Islet antigen-2 (IA-2) antibodies. Total cholesterol was considered high if above 200 mg/dL, LDL if above 130 mg/dL. Data about initial presentation with diabetes ketoacidosis (DKA) was available for only two centers.

Statistical analysis

Demographic, clinical, vaccination and biochemical characteristics of the participants were summarized in percentages for categorical variables. For continuous variables, the data were reported in means (with standard deviation (SD)) if normally distributed and in medians (25–75 percentiles) if not normally distributed.

The impact of the COVID-19 epidemic was assessed by comparing the annual numbers of new-onset T1D cases, using linear regression for trend analysis, from 2018 to 2021. Median levels of glucose, HbA1c and fasting C-peptide at T1D diagnosis were analyzed using Kruskal-Wallis test, due to the non-normal distribution of the data. In these metabolic analyses, we used the entire dataset, from 2017 to 2022.

The annual incidence of DKA cases was assessed using linear regression. The risk factor assessment for DKA at time of T1D diagnosis, with prior COVID-19 as the main variable of interest, was done using logistical regression and reported as odds ratios (OR). Concurrent COVID-19 identified at the time of T1D diagnosis was included in the prior COVID-19 group, as test results can remain positive for some time. In the multivariate model, we included co-variables previously investigated in relation to DKA such as age, gender, family history of T1D and HbA1c [20, 21]. Age was included as a continuous variable. HbA1c was grouped (≤ 12.0 , $> 12.0\%$) due to non-linearity, with the 12.0% cut-off chosen for being close to the overall HbA1c median and the fact that values above that indicate severe glycaemic dysregulation.

All data were analyzed in STATA 15 software (Stata-Corp LLC, Texas, USA).

Results

Demographic characteristics

A total of 574 patients with new-onset T1D were included in this analysis. Due to the centers included, the vast majority were children below 18 years of age, i.e.

92.3%. (530/574). The mean ages for child and adult T1D cases were 9.1 (SD 4.4) and 32.8 (SD 13.6) years, respectively. Slightly more males than females were included, i.e. 57.8% (331/573). The sex of one patient was not available. A family history of T1D was reported in 20.9% (113/541) of the participants. A total of 8.6% (42/487) reported prior (or concurrent) COVID-19 infection at T1D diagnosis. The majority, 81.1% (413/509), had previously been BCG vaccinated. The results are reported in Table 1.

Number of new-onset T1D cases

Overall, in the eight centers with complete data (2018–2021), we observed a numerical increase in new-onset T1D cases during the study years. However, this did not reach statistical significance, i.e., 90 cases in 2018, 90 cases in 2019, 112 in 2020 and 100 in 2021 (P for trend=0.36). The increase was largely driven by two sites, Faro (CHUA) and Dona Estefânia (CHULC) hospitals, which observed 2.6–2.8 times as many T1D cases in 2020 compared to 2019. The other hospitals reported unchanged annual T1D rates, or even lower in 2020. The annual T1D numbers from 2018 to 2021 for the eight centers combined are illustrated in Fig. 1.

In terms of individual calendar months, the highest T1D case numbers were observed in January 2020 and January 2021 (18 cases in each month). The lowest rate was in March 2020, with only two new-onset T1D cases. The number of new-onset T1D cases per individual month from 2018 to 2021 is illustrated in Fig. 2.

The Centro Hospitalar de Vila Nova de Gaia/Espinho was not included in the case trend analysis, nor in Figs. 1 and 2, due to incomplete data from 2021. The numbers of new T1D cases at the center were 12 (2018), 17 (2019), 8 (2020), i.e. no increase was observed during the first year of the pandemic.

Metabolic parameters

The glucose, HbA1c and fasting C-peptide values at the time of T1D diagnosis from the individual hospital units are shown in Table 1, and the trend over time is illustrated in Figs. 3, 4 and 5. Overall, the median values were 454 mg/dL (356–568) for glucose, 11.8% (10.1–13.4) for HbA1c and 0.50 $\mu\text{g/L}$ (0.30–0.79) for fasting C-peptide. No significant changes in the three biochemical analyses were observed during the entire study period from 2017 to 2022, i.e. $P=0.32$, $P=0.68$ and $P=0.20$, respectively.

Overall, 81.7% (385/471) of the patients were GAD-antibody positive. This proportion tended to increase during the COVID-19 pandemic, compared to the time before, i.e. 85.6% (178/208) vs. 78.7% (207/263) ($P=0.06$). For IA-2 antibodies, a total of 73.3% (222/303) were positive. This proportion did not increase during the

Table 1 Patients in Portugal presenting with newly diagnosed type 1 diabetes

	Hospital Espírito Santo N=43	Centro Hospitalar de Leiria N=34	Hospital Santa Maria Maior N=21	Hospital Dona Estefânia (CHULC) N=60	Hospital de Santa Maria N=107	Hospital de Faro (CHUA) N=78	Hospital de Portimão e Lagos (CHUA) N=50	Centro Hospitalar de Coimbra (CHUC) N=127	Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E) N=54
Demographic and clinical data									
Age (years) ¹	8.58 (4.71)	10.3 (4.97)	11.2 (3.17)	7.97 (4.02)	9.06 (4.52)	8.96 (4.22)	32.8 (13.6)	9.29 (4.48)	8.78 (4.12)
Male sex (%; n/N)	56% (24/43)	53% (18/34)	52% (11/21)	53% (32/60)	64% (68/106)	46% (36/78)	66% (33/50)	63.0% (80/127)	53.7% (29/54)
Weight (kg) ¹	31.7 (15.8)	37.3 (18.3)	38.9 (10.2)	29.1 (12.7)	34.0 (17.8)	34.8 (16.9)	63.2 (15.4)	37.0 (18.6)	36.2 (17.8)
Height (cm) ¹	131.4 (29.2)	148.4 (27.1)	150.1 (15.5)	131.4 (25.2)	135.9 (28.6)	136.6 (27.3)	167.9 (10.2)	138 (27.6)	136.7 (25.8)
Systolic BP (mmHg) ¹	111.1 (13.4)	114.8 (12.2)	112.2 (10.3)	106.0 (19.5)	110.3 (11.6)	109 (12.8)	113 (14.5)	104.6 (12.9)	105.1 (12.1)
Diastolic BP (mmHg) ¹	69.8 (11.3)	70.4 (10.7)	64.9 (8.4)	66.8 (9.8)	64.4 (10.3)	68.4 (10.7)	72.5 (12.2)	60.8 (9.53)	57.8 (6.35)
Family history of T1D (%; n/N)	28% (12/43)	32% (11/34)	-	34% (18/53)	22.4% (24/107)	19% (15/78)	16% (8/50)	11.0% (14/127)	21% (11/52)
Other comorbidities (%; n/N)	28% (12/43)	-	29% (6/21)	26% (15/58)	10.3% (11/107)	12% (9/78)	40% (19/48)	29.1% (37/127)	22% (11/51)
COVID-19 prior to T1D (%; n/N)	-	-	5% (1/21)	4% (2/53)	8.5% (9/106)	13% (10/78)	8% (4/50)	11.8% (15/127)	2% (1/52)
Vaccination status									
COVID-19 vaccination (%; n/N)	-	-	-	-	-	-	18% (9/50)	-	-
BCG vaccination (%; n/N)	72.1% (31/43)	88.2% (30/34)	95.2% (20/21)	78% (47/60)	84.8% (89/105)	80.8% (63/78)	58.5% (24/41)	85.8% (109/127)	-
Biochemical data									
Glucose (mg/dl) ²	449 (388–515)	431 (361–663)	523 (421–556)	455 (359–539)	458 (370–600)	398 (310–498)	343 (254–500)	483 (381–595)	482 (375–580)
HbA1c (%), ²	11.6 (10.2–13.4)	11.8 (10.1–13.2)	10.4 (9.3–11.7)	11.7 (10.4–13.4)	12.3 (11.0–14.2)	11.3 (9.2–13.2)	12.2 (10.3–14.0)	11.9 (10.3–13.4)	11.6 (9.4–13.6)
Fasting C-peptide (µg/L) ²	0.60 (0.35–1.0)	0.50 (0.30–0.75)	0.36 (0.23–0.59)	0.30 (0.20–0.40)	0.57 (0.40–0.87)	0.50 (0.30–0.90)	0.50 (0.20–0.70)	0.49 (0.30–0.70)	0.63 (0.52–0.96)
LDL (mg/dL) ²	85 (68–127)	111 (83–163)	87.5 (79–102)	111 (92–147)	74 (61–91)	98 (78–116)	112 (85–140)	100 (81–125)	-
Total cholesterol (mg/dL) ²	182 (140–211)	198 (168–264)	172 (155–203)	177 (153–201)	151 (135–162)	164 (143–189)	178 (149–212)	169 (147–210)	-
Presenting with DKA (%; n/N)	-	-	-	-	55.1% (59/107)	-	34% (17/50)	-	-
GAD antibody positive (%; n/N)	61% (25/41)	75% (21/28)	86% (18/21)	65% (36/55)	96.0% (97/101)	88% (58/66)	62% (26/42)	88.9% (104/117)	-
IA-2 antibody positive (%; n/N)	63% (22/35)	-	89% (8/9)	67% (34/51)	75.0% (75/100)	80% (35/44)	54% (7/13)	80% (40/50)	100% (1/1)

¹ Mean values (SD)

² Median values (25–75 percentiles)

Note: For abbreviations: CHULC denotes Centro Hospitalar Universitário de Lisboa Central, CHUA Centro Hospitalar Universitário Do Algarve, CHUC Centro Hospitalar e Universitário de Coimbra, CHVNG/E Centro Hospitalar de Vila Nova de Gaia/Espinho; BP Blood pressure, T1D Type 1 diabetes, COVID-19 coronavirus disease 2019, BCG Bacillus Calmette-Guérin, HbA1c glycated haemoglobin, LDL low density lipoprotein, DKA diabetes ketoacidosis, GAD glutamic acid decarboxylase, IA-2 islet antigen 2.

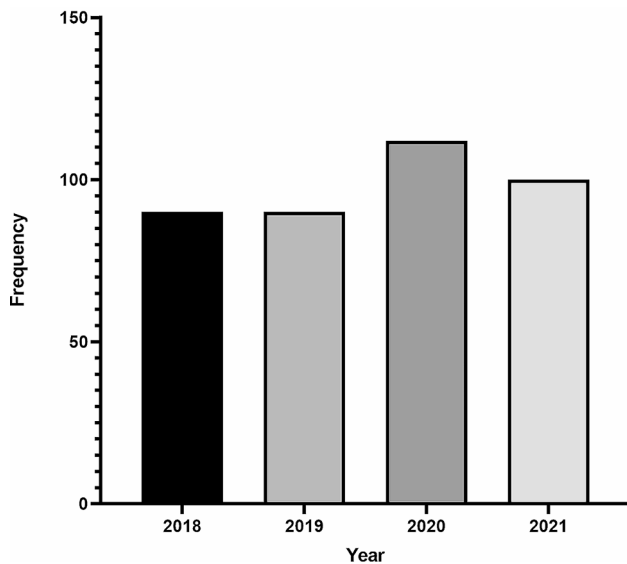


Fig. 1 Number of newly diagnosed T1D patients per year (2018–2021). Note The figure only shows 2018–2021, as these were full calendar years. Also, it only includes the eight centers with complete data (i.e. Santa Maria Hospital in Lisbon, Dona Estefânia Hospital in Lisbon, Centro Hospitalar in Leiria, Hospital Santa Maria Maior in Barcelos, Hospital Espírito Santo in Évora, Centro Hospitalar Universitário do Algarve in Faro, the Pediatric Hospital in Coimbra, Hospital de Portimão e Lagos at the Algarve Coast).

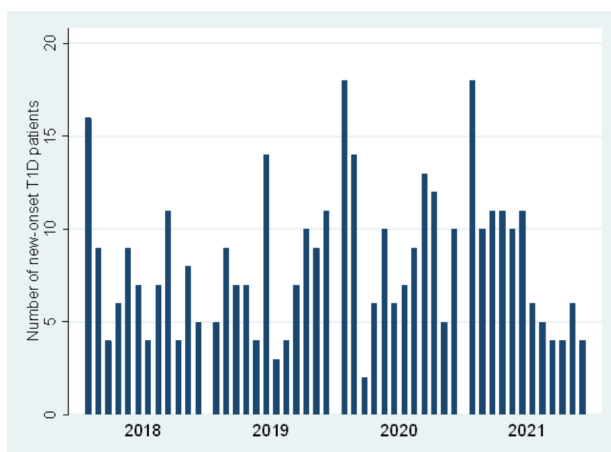


Fig. 2 Number of newly diagnosed T1D patients per individual calendar month (2018–2021)

pandemic, compared to the years before, 70.0% (105/150) vs. 76.5% (117/153) ($P=0.20$).

The proportion of T1D patients with elevated total cholesterol and LDL levels did not increase significantly during the pandemic, compared to the years before. For cholesterol, the proportion was 27.6% (50/181) vs. 21.7% (55/254) ($P=0.15$). For LDL, it was 20.8% (36/173) vs. 16.9% (42/248) ($P=0.31$).

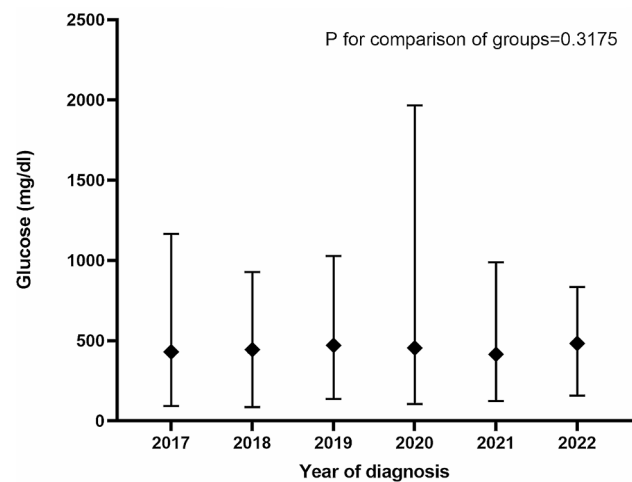


Fig. 3 Glucose levels at T1D diagnosis from 2017 to 2022

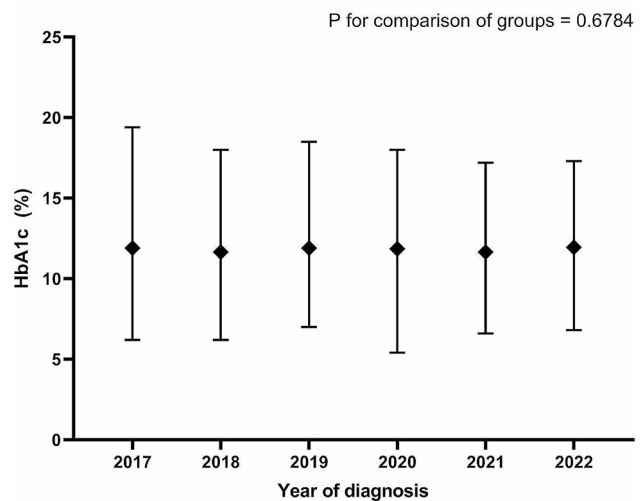


Fig. 4 HbA1c levels at T1D diagnosis from 2017 to 2022

DKA episodes and risk factor analysis

DKA data were available from a subset of 157 patients from two centers, i.e. children from Hospital Santa Maria in Lisbon and adults from Hospital de Portimão e Lagos (CHUA). The overall proportion of DKA episodes out of the total number of new T1D cases was 48.4% (76/157). The annual DKA incidence did not change during the full calendar years from 2018 to 2021 ($P=0.68$).

The DKA risk factor analysis is shown in Table 2 and comprised all 157 patients with available DKA data (155 in the multivariate analysis). In both the univariate ($P=0.68$) and multivariate model ($P=0.65$), we could not establish prior COVID-19 infection as a risk factor for DKA. In the multivariate model, the OR for DKA decreased with higher age (0.97, 0.95–1.00), meaning that young age was a risk factor for DKA. There was a

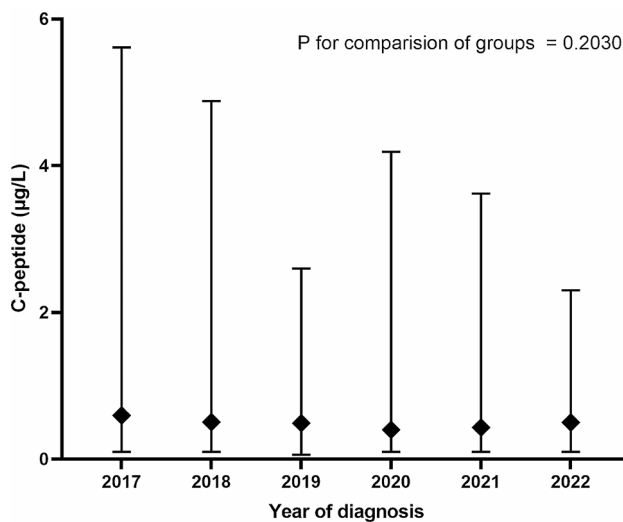


Fig. 5 Fasting C-peptide levels at T1D diagnosis 2017 to 2022

Table 2 Risk factor analysis for diabetes ketoacidosis at first presentation

	Univariate		Multivariate N= 155	
	OR (CI)	P	OR (CI)	P
Age (years)¹	0.98 (0.95–1.00)	0.05	0.97 (0.95–1.00)	0.04
Gender				
Female	1.00 (ref)	-	1.00 (ref)	-
Male	1.09 (0.57–2.11)	0.79	1.10 (0.55–2.20)	0.78
T1D family disposition				
No	1.00 (ref)	-	1.00 (ref)	-
Yes	0.57 (0.26–1.27)	0.17	0.52 (0.23–1.17)	0.11
HbA1c				
≤12.0% (ref)	1.00 (ref)	-	1.00 (ref)	-
> 12.0%	1.28 (0.68–2.42)	0.44	1.37 (0.71–2.65)	0.36
Prior COVID-19 infection				
No	1.00 (ref)	-	1.00 (ref)	-
Yes	1.27 (0.41–3.96)	0.68	1.32 (0.41–4.27)	0.65

¹ Included as a continuous variable

Note For abbreviations used, OR denotes odds ratio, CI 95% confidence interval, T1D Type 1 diabetes, HbA1c glycated hemoglobin, COVID-19 coronavirus disease 2019

tendency of family history of T1D being a protective factor for DKA (0.52, 0.23–1.17).

Discussion

Main findings

Though a slight numerical increase was observed in new-onset T1D in 2020 and 2021, compared to the previous years, this did not reach statistical significance. Nor did glucose, HbA1c or fasting C-peptide levels and incidence of DKA at T1D diagnosis change significantly over

the study years. As such, a strong association between COVID-19 and T1D was not confirmed.

Strengths and limitations

Our study is the first national investigation of the relationship between new-onset T1D and COVID-19 in Portugal. It comprises a large dataset with considerable geographic variation and a T1D diagnosis confirmed at the individual level. In this context, the presence of GAD antibodies in 82% of the participants equals what has previously been reported for T1D patients [1], as does any family history of T1D in one fifth of the patients [22]. Importantly, apart from T1D incidence data, it also provides information on initial glycemic levels and fasting C-peptide across the years, as well as the number of and risk factors for presentation with DKA.

Our study does, however, have some limitations. Notably, we did not have access to SARS-CoV-2 antibody measurements. Furthermore, a detailed COVID-19 test history (including positive PCR or Quick-test result) may not always have been confirmed at the time of T1D diagnosis, and the 8.6% of patients with previous or concurrent COVID-19 could therefore be an underestimation. This naturally affects our possibility to conduct correlation analyses on individual patient level.

Our analysis only comprises data from the initial presentation, including fasting C-peptide. Hypothetically, infection with the SARS-CoV-2 virus may affect the progression of T1D, inducing a more rapid loss of endogenous insulin production through β -cell apoptosis, but prospective longitudinal studies are necessary to test this hypothesis.

Our investigation of new T1D cases only includes absolute numbers from the individual hospitals, i.e. not relative to the background population. T1D incidence rates have therefore not been reported. Changes in patient uptake areas could have affected the numbers. However, we have no knowledge of any major changes in procedures here.

While symptoms at diagnosis were recorded for all centers, data on whether there was ketoacidosis could only be retrieved from a subset of two hospitals, which limits the precision and power of this analysis.

Finally, our data is largely based on pediatric T1D patients. We can therefore only make very limited assumptions in terms of adults with new-onset T1D. However, the highest incidence of T1D is usually seen before the age of 18 years [23].

Consistency with previous findings

Portugal recorded the first cases of COVID-19 in early March 2020. As in other European countries, and despite strict control measures, a rapid increase in COVID-19 cases were observed over the following weeks [24].

Several severe COVID-19 waves were observed, and a population-based study reported a high SARS-CoV-2 seroprevalence of 17.3% in March 2021 [25].

While we did not observe an overall significant increase in the number of T1D cases during the COVID-19 pandemic, we did note a substantial rise at two individual centers. One was the Dona Estefânia Hospital in Lisbon, where an investigation by *Caetano et al.* from 2022 had previously examined COVID-19 in relation to new-onset T1D in children from March 2020 to March 2021, and compared to the years before [26]. Our findings corroborated the previously reported increase in T1D cases from that center. The two sites, Dona Estefânia Hospital in Lisbon and Centro Hospitalar Universitário do Algarve in Faro, were geographically distinct and both rather large. We could not identify any changes in procedures or patient uptake which could explain the increases.

Although viral infections have long been suggested as having a role in T1D development, studies concerning SARS-CoV-2 infection as a precipitating factor are currently pointing in different directions. Overall, our study is in line with recent large register studies from Scotland [12] and Denmark [17] that did not find evidence of a link between PCR confirmed SARS-CoV-2 and incidence of T1D. The Danish child study is interesting in this regard, as Denmark had one of the highest test frequencies in the world [17]. Other large studies, e.g. from the U.S. [11, 27], have, however, observed a possible association between the COVID-19 pandemic and diabetes development. A German register study among children and adolescents reported a peaking T1D incidence about 3 months after the peak in COVID-19 cases, which could be due to direct viral effects on β -cell function. Indirect factors, possibly related to control measures and thereby altered or delayed exposures to other infections or lifestyle changes, were however considered more likely [28].

Though it did not reach statistical significance, more T1D cases were seen in our study during 2020 and 2021, compared to the two previous years. This would, however, not necessarily be indicative of an association with SARS-CoV-2 infection per se, as child T1D rates have been gradually increasing for many years, even before the pandemic [29]. Thus, a publication based on data from the SWEET register concluded that the slope of rise in pediatric T1D cases had remained unchanged during the pandemic [15]. In the Danish study investigating the entire population below 30 years, an increase in T1D cases was noted in April–June 2021 compared to April–June 2015–2019, but based on SARS-CoV-2 test results this was not attributed to the virus [18]. A study from Japan reported an increasing trend in pediatric T1D cases over the past 23 years – a trend unchanged by the COVID-19 pandemic [30].

One reason for the conflicting results may be due to the various study designs applied. For instance, the U.S. studies used data derived from health care claim databases. In contrast, the two studies from Denmark [17, 18] and the one from Scotland [12] were based on national health registries. Our present investigation from Portugal represents yet another type, compiling clinical data from individual hospital units to make an overall estimate.

Importantly, the COVID-19 pandemic affected countries in various ways, with different lock-down schemes being implemented. In Portugal, very strict control measures were implemented, with full lock-downs occurring in both March 2020 and January 2021. Apart from COVID-19 cases, only the most essential in-person medical appointments were allowed, with teleconsultations instead being encouraged. This likely resulted in a high proportion of 34% of people reporting unmet health care needs during the early pandemic, a proportion that was significantly higher than in many other European countries [31]. Naturally, these control measures also affected the transmission of other viral infections that may in some instances trigger T1D development. This could affect comparisons between populations. Clear changes in the seasonality of T1D diagnosis was observed elsewhere, with more cases recorded during the summer of 2020 compared to previous years [15]. In our data from Portugal, we confirmed the previous observed pattern of more T1D cases during the colder winter months, with most cases being detected in January and February. Others have noted how the mutating strains of SARS-CoV-2 and behavioral changes such as social distancing and increased hygienic practices complicate the interpretation of results in relation to T1D [30]. Finally, there may also be genetic differences in COVID-19 susceptibility [30].

Interestingly, the authors from the previous Portuguese study on T1D and COVID-19 had identified a higher proportion of severe DKA and intensive care unit admissions during the first year of the pandemic [26]. In Germany, an increase in DKA during the early pandemic was reported among children with new-onset T1D, which lasted even after the number of COVID-19 cases had dropped. Here, it was concluded that concern of infection had led to a prolonged avoidance of necessary health care, resulting in more DKA cases [32]. In Finland, more cases of severe DKA were observed during the pandemic, a finding considered related to changes in parental behavior and health care accessibility [33]. A similar finding of an increased rate of severe DKA cases was done in Poland [34]. We did not have data on DKA severity, but we did not find a higher overall DKA incidence during the epidemic, nor did previous COVID-19 affect the risk of DKA in the multivariate analysis. However, our DKA analysis may have been limited by low numbers

and only from two hospitals. In our data, we noted the lowest monthly rate of new-onset T1D in March 2020 (only two cases), supporting the fact that T1D diagnoses were delayed at that time. In the multivariate analysis, we observed higher odds of DKA in young children, which may be due to early diabetes symptoms being harder to recognize here. A family history of T1D tended to reduce the risk of DKA, which could be due to better parental awareness of diabetes and hence earlier detection [35].

Noteworthy, BCG vaccination was previously until 2016 part of the standard vaccination programme in Portugal. In our study, 81% of the patients were BCG vaccinated. It has been suggested how BCG can ameliorate the severity of viral respiratory infections [36], likely through *non-specific* beneficial effects on the innate immune system [37]. In the U.S., a study among adult T1D patients showed a protective effect of multiple BCG vaccinations on SARS-CoV-2 infection [38]. This should be considered when comparing to settings where BCG vaccination has not been routinely applied, and it would be interesting to compare T1D incidence in more countries with and without obligatory BCG vaccination.

Also of note, the proportion of GAD positive T1D patients tended to increase during the pandemic (after the first 1st of March, 2020). While the change was quite small in percentage, i.e. 86% vs. 79%, it could be hypothesized that this may have been due to changes in viral triggers for autoimmunity. A similar trend was, however, not observed for IA-2 antibodies.

Finally, others have observed how COVID-19 may cause dyslipidaemia, possibly both through direct inflammatory pathways and also indirectly through behavioral changes [39]. Though we observed a slight increase in T1D patients with elevated cholesterol and LDL levels during the pandemic, this did not reach statistical significance. The predominantly young age of our participants, however, needs to be taken into account.

Implications

Our investigation contributes to the ongoing debate on whether T1D development can be triggered by the SARS-CoV-2 infection. Essentially, it calls for further studies, both in local and more global contexts, involving multi-center setups to increase the number of participants. The severity of COVID-19 and T1D at the time of diagnosis should also be examined further in clinical studies.

Though we did not find a significant correlation between COVID-19 and new onset T1D, we cannot exclude that it does in fact exist, as smaller trends may not have been captured by our analysis. For instance, in the Canadian cohort study it was concluded that COVID-19 may have contributed to a 3–5% excess burden of diabetes at the population level [16]. That study mainly focused on non-insulin-dependent diabetes, as

there were few cases of insulin-dependent diabetes (i.e. T1D).

While a considerable number of studies have investigated the association between T1D incidence and the COVID-19 epidemic, both in adults and in children, investigations concerning the course of new-onset T1D among SARS-CoV-2 infected patients are sparse. In our study, we report on fasting C-peptide levels at the time of diagnosis, but not serial measurements over time. Future studies should take this into consideration, as the pace of loss of β -cell function in T1D has important clinical implications.

Conclusion

We could not establish a significant temporal association between the COVID-19 pandemic and T1D incidence, nor in terms of changes in key metabolic parameters such as glucose, HbA1c and fasting C-peptide at the time of diagnosis. Frequency of DKA at the time of T1D diagnosis was not affected either. Any strong association between SARS-CoV-2 and T1D was therefore not supported.

Abbreviations

ACE-2	Angiotensin-converting enzyme 2
BCG	Bacillus Calmette-Guérin
COVID-19	Coronavirus disease 2019
GAD	Anti-glutamic acid decarboxylase
DKA	Diabetes ketoacidosis
HbA1c	Glycated hemoglobin
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
T1D	Type 1 diabetes

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Author contributions

M.B.A., C.B.J., K.H. and E.C. designed the study. J.D.S. assisted with the overall data collection and aggregation, as well as obtaining the necessary ethical approvals. R.D., A.R.C., I.F., A.R., P.R., B.S., G.L., S.R., I.F., S.A., M.M.F.C., G.G., S.A., M.F., T.S., M.R., E.F., L.A., A.B., A.M.F., D.A., C.G., A.L.L., M.L.A.L., M.L.S., J.S.C. collected and entered the data at the various participating hospital units. M.B.A. wrote the first manuscript draft and all authors approved the final version.

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Data availability

The data can be made available by contacting the corresponding author upon reasonable request, provided approval by the study senior author and participating hospital units.

Declarations**Ethical approval**

The study was approved by the local ethical committees or institutional review boards from each participating hospital center in Portugal, here listed below: Comissão de Ética para a Saúde do CHUC, E.P.E. (SF.15/2021, Coimbra). Comissão de Ética do Centro Académico de Medicina de Lisboa (171/21, Hospital Santa Maria). Comissão de Ética para a Saúde do CHL, E.P.E. (Ata nº 05 de 2021.05.13 & 27/2021, Leiria). Comissão de Ética para a Saúde do Hospital Santa Maria Maior, E.P.E. (Barcelos). Comissão de Ética do HESE, E.P.E., Comissão de Ética para a Saúde do CHUA, E.P.E. (Ata nº 44 de 16.11.2021, Évora). Comissão de Ética para a Saúde do CHUA, E.P.E. (145/22, Algarve (Faro, Portimão, Lagos)). Comissão de Ética para a Saúde do CHVNG/E, E.P.E. (117/2021, Vila Nova de Gaia). Comissão de Ética para a Saúde do CHULC, E.P.E. (1104/2021, Hospital Dona Estefânia). The data were anonymized in terms of personal identifiers. The need for individual consent was waived for the collected routine clinical data by the ethics committees of Comissão de Ética para a Saúde do CHUC, E.P.E.; Comissão de Ética do Centro Académico de Medicina de Lisboa; Comissão de Ética para a Saúde do CHL, E.P.E.; Comissão de Ética para a Saúde do Hospital Santa Maria Maior, E.P.E.; Comissão de Ética do HESE, E.P.E.; Comissão de Ética para a Saúde do CHUA, E.P.E.; Comissão de Ética para a Saúde do CHUA, E.P.E.; Comissão de Ética para a Saúde do CHVNG/E, E.P.E.; Comissão de Ética para a Saúde do CHULC, E.P.E. The study (along with parallel investigations in Denmark) had been registered on www.ClinicalTrials.gov (NCT04623697).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Katsarou A, Gudbjornsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. *Nat Rev Dis Primers*. 2017;3:17016.
2. Karaoglan M, Eksi F. The coincidence of newly diagnosed type 1 diabetes Mellitus with IgM antibody positivity to enteroviruses and respiratory tract viruses. *J Diabetes Res*. 2018;2018:8475341.
3. Lemos JRN, Hirani K, von Herrath M. Immunological and virological triggers of type 1 diabetes: insights and implications. *Front Immunol*. 2023;14:1326711.
4. Filippi CM, von Herrath MG. Viral trigger for type 1 diabetes: pros and cons. *Diabetes*. 2008;57(11):2863–71.
5. Gerasimidi Vazeou A, Kordonouri O, Witsch M, Hermann JM, Forsander G, de Beaufort C et al. Seasonality at the clinical onset of type 1 diabetes-lessons from the SWEET database. *Pediatr Diabetes*. 2016;17 Suppl 23:32–7.
6. Patterson CC, Gyurus E, Rosenbauer J, Cinek O, Neu A, Schober E, et al. Seasonal variation in month of diagnosis in children with type 1 diabetes registered in 23 European centers during 1989–2008: little short-term influence of sunshine hours or average temperature. *Pediatr Diabetes*. 2015;16(8):573–80.
7. World Health Organization. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. 2023.
8. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell*. 2020;27(1):125–36. e7.
9. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in Pancreas May cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol*. 2020;18(9):2128–30. e2.
10. Unsworth R, Wallace S, Oliver NS, 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(11):e170–1.
11. Barrett CE, Koyama AK, Alvarez P, Chow W, Lundeen EA, Perrine CG, et al. Risk for newly diagnosed diabetes > 30 days after SARS-CoV-2 infection among persons aged < 18 years - United States, March 1, 2020-June 28, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(2):59–65.
12. McKeigue PM, McGurnaghan S, Blackburn L, Bath LE, McAllister DA, Caparrotta TM, et al. Relation of Incident Type 1 diabetes to recent COVID-19 infection: Cohort Study using e-Health record linkage in Scotland. *Diabetes Care*. 2023;46(5):921–8.
13. Rahmati M, Keshvari M, Mirnasuri S, Yon DK, Lee SW, Il Shin J, et al. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: a systematic review and meta-analysis. *J Med Virol*. 2022;94(11):5112–27.
14. D'Souza D, Empringham J, Pechlivanoglou P, Ulerly EM, Cohen E, Shulman R. Incidence of diabetes in children and adolescents during the COVID-19 pandemic: a systematic review and Meta-analysis. *JAMA Netw Open*. 2023;6(6):e2321281.
15. Reschke F, Lanzinger S, Herczeg V, Prahalad P, Schiaffini R, Mul D, et al. The COVID-19 pandemic affects seasonality, with increasing cases of New-Onset type 1 diabetes in children, from the Worldwide SWEET Registry. *Diabetes Care*. 2022;45(11):2594–601.
16. Naveed Z, Velasquez Garcia HA, Wong S, Wilton J, McKee G, Mahmood B, et al. Association of COVID-19 infection with Incident Diabetes. *JAMA Netw Open*. 2023;6(4):e238866.
17. Noorzae R, Junker TG, Hviid AP, Wohlfahrt J, Olsen SF. Risk of type 1 diabetes in children is not increased after SARS-CoV-2 infection: a nationwide prospective study in Denmark. *Diabetes Care*. 2023;46(6):1261–4.
18. Zareini B, Sorensen KK, Eiken PA, Fischer TK, Kristensen PL, Lendorf ME, et al. Association of Coronavirus Disease 2019 and development of type 1 diabetes: a Danish Nationwide Register Study. *Diabetes Care*. 2023;46(8):1477–148218.
19. Pereira SM, Barreto FR, de Souza RA, de Souza Teles Santos CA, Pereira M, da Paixao ES, et al. Previous BCG vaccination is associated with less severe clinical progression of COVID-19. *BMC Med*. 2023;21(1):145.
20. Lee HJ, Yu HW, Jung HW, Lee YA, Kim JH, Chung HR, et al. Factors Associated with the Presence and Severity of Diabetic Ketoacidosis at diagnosis of type 1 diabetes in Korean children and adolescents. *J Korean Med Sci*. 2017;32(2):303–9.
21. Nakhla M, Rahme E, Simard M, Larocque I, Legault L, Li P. Risk of ketoacidosis in children at the time of diabetes mellitus diagnosis by primary caregiver status: a population-based retrospective cohort study. *CMAJ*. 2018;190(14):E416–21.

22. Parkkola A, Harkonen T, Ryhanen SJ, Ilonen J, Knip M, Finnish Pediatric Diabetes R. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. *Diabetes Care*. 2013;36(2):348–54.
23. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am*. 2010;39(3):481–97.
24. Borges V, Isidro J, Trovao NS, Duarte S, Cortes-Martins H, Martiniano H, et al. SARS-CoV-2 introductions and early dynamics of the epidemic in Portugal. *Commun Med (Lond)*. 2022;2:10.
25. Canto ECL, Gomes A, Serrano M, Pereira AHG, Ribeiro R, Napoleao P, et al. Longitudinal SARS-CoV-2 seroprevalence in Portugal and antibody maintenance 12 months after infection. *Eur J Immunol*. 2022;52(1):149–60.
26. Caetano FB et al. Impact of COVID-19 in New-Onset Type 1 Diabetes Mellitus in a Large Portuguese Pediatric Diabetes Center. *Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo*. 2022. 17 (3–4).
27. Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Association of SARS-CoV-2 infection with New-Onset type 1 diabetes among Pediatric patients from 2020 to 2021. *JAMA Netw Open*. 2022;5(9):e2233014.
28. Kamrath C, Rosenbauer J, Eckert AJ, Siedler K, Bartelt H, Klose D, et al. Incidence of type 1 diabetes in children and adolescents during the COVID-19 pandemic in Germany: results from the DPV Registry. *Diabetes Care*. 2022;45(8):1762–71.
29. Patterson CC, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. *Diabetologia*. 2019;62(3):408–17.
30. Matsuda F, Itonaga T, Maeda M, Ihara K. Long-term trends of pediatric type 1 diabetes incidence in Japan before and after the COVID-19 pandemic. *Sci Rep*. 2023;13(1):5803.
31. European Commission. State of Health in the EU. Portugal Country Health Profile; 2021.
32. Kamrath C, Rosenbauer J, Eckert AJ, Pappa A, Reschke F, Rohrer TR et al. Incidence of COVID-19 and Risk of Diabetic Ketoacidosis in New-Onset type 1 diabetes. *Pediatrics*. 2021;148(3).
33. Salmi H, Heinonen S, Hastbacka J, Laaperi M, Rautiainen P, Miettinen PJ, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2022;107(2):180–5.
34. Pietrzak I, Michalak A, Seget S, Bednarska M, Ben-Skowronek I, Bossowski A, et al. Diabetic ketoacidosis incidence among children with new-onset type 1 diabetes in Poland and its association with COVID-19 outbreak-two-year cross-sectional national observation by PolPeDiab Study Group. *Pediatr Diabetes*. 2022;23(7):944–55.
35. Lokulo-Sodipe K, Moon RJ, Edge JA, Davies JH. Identifying targets to reduce the incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in the UK. *Arch Dis Child*. 2014;99(5):438–42.
36. Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S, Antonakos N, Kotsaki A, Dominguez-Andres J, et al. Activate: Randomized Clinical Trial of BCG vaccination against infection in the Elderly. *Cell*. 2020;183(2):315–23. e9.
37. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, et al. Trained immunity: a program of innate immune memory in health and disease. *Science*. 2016;352(6284):aaf1098.
38. Faustman DL, Lee A, Hostetter ER, Aristarkhova A, Ng NC, Shpilsky GF, et al. Multiple BCG vaccinations for the prevention of COVID-19 and other infectious diseases in type 1 diabetes. *Cell Rep Med*. 2022;3(9):100728.
39. Xu E, Xie Y, Al-Aly Z. Risks and burdens of incident dyslipidaemia in long COVID: a cohort study. *Lancet Diabetes Endocrinol*. 2023;11(2):120–8.

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