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Characteristics of New-Onset Paediatric Type 1 Diabetes in the COVID-19 Pandemic – A Multicentre Perspective

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Keywords: Paediatric Type 1 diabetes; Diabetic Ketoacidosis; Children; COVID-19; SARS-CoV-2.

Abstract

Objectives: To characterise the features of children diagnosed with new onset type 1 diabetes in the COVID-19 pandemic, exploring the incidence of Diabetic Ketoacidosis (DKA) and investigating any association with SARS-CoV-2.

Methods: We analysed the characteristics of children with new onset type 1 diabetes aged 6 months-17 years presenting from January to July 2020 to 12 Paediatric Diabetes Units (PDUs) in the UK. Data from the same time period in 2019 was compiled for comparison.

Results: There was a statistically significant increase in the number of children with new-onset type 1 diabetes presenting with DKA in 2020 when compared to 2019 (79 versus 49, $p < 0.05$). There was also an increase in the number of children presenting in severe DKA in 2020 when compared to 2019 (36 versus 16). The percentage of children presenting with DKA with new onset type 1diabetes in 2020 showed a significant increase when compared to the previous 4 years. 25-32% of children who presented with new onset type 1 diabetes presented with DKA between 2016 to 2019. In 2020, 44% of children with new onset diabetes presented with DKA. The incidence of new onset type 1 diabetes from January to July 2020 was similar to the previous 4 years in 10 PDUs. An apparent increase in 2020 was noted in two units, both were from inner city localities with a highly diverse ethnic mix. Two children with new onset type 1 diabetes presented with severe DKA and shock and tested positive for SARS-CoV-2 on nasopharyngeal swabs, providing evidence of a link with diabetes and SARS-CoV-2. COVID-19 antibodies were done in 11 children in 2020 and was negative in all.

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Conclusion: There was increased incidence and severity of DKA during the study period in 2020 compared to the previous four years. It is vital to emphasise the early recognition of DKA in children with new-onset diabetes particularly in view of the increased incidence in the pandemic. 2020 was a high incidence year for children with new onset diabetes compared to the previous four years. However our study did not provide evidence that the COVID-19 pandemic is leading to a marked increase in incidence of pediatric type 1 diabetes.

Introduction

Paediatric diabetes has been the focus of attention during the COVID-19 pandemic for several reasons. There was a reported increase in the incidence of new-onset type 1 paediatric diabetes in the pandemic and concerns that the incidence was related to an infection or a dysregulated immune response to SARS-CoV-2 [1]. Studies have also reported concerns about delayed presentations to the Emergency Department (ED) due to parental fears of SARS-CoV-2, resulting in an increase in the incidence and severity of diabetic ketoacidosis in children with new-onset diabetes [2,3].

The COVID-19 pandemic has resulted in significant changes in the healthcare system. Whilst adult services were overwhelmed with sick patients, there was an unprecedented decline in pediatric attendances [4,5]. This in turn led to concerns about the collateral damage to children due to delayed presentations to the ED [2]. The most frequently reported delayed presentation was the new diagnosis of diabetes mellitus [2,3]. Diabetic Ketoacidosis (DKA) is an acute life-threatening complication of diabetes. Early diagnosis of paediatric diabetes is essential to allow treatment to start as soon as possible to prevent DKA and in the interest of better long-term glycaemic control. If it is proven that the perceived increased incidence of paediatric diabetes is related to an infection with SARS-CoV-2, this has implications for enhancing public and clinician awareness of diabetes in children resulting in early recognition and prevention of DKA.

Materials and methods

We compiled and analysed multicentre, retrospective, anonymised data of new-onset type 1 diabetes during the COVID-19 pandemic in children aged 6 months - 17 years from 12 Paediatric Diabetes Units (PDUs) across South London, Kent, Brighton, and North East London. We compared the characteristics of 178 children presenting with new-onset type 1 diabetes between January and July 2020 (time period of interest) with those of 150 children who presented during the same period in 2019. Each PDU has a defined geographical area and paediatric population which has not changed over the data collection period. Each centre also provided four years of retrospective data for total numbers of new-onset type 1 diabetes to account for the yearly and seasonal variation in incidence and DKA.

Data was collected from centres using a consensus data collection template incorporating the characteristics of new-onset type 1 diabetes in children. These characteristics included age at presentation, gender, ethnicity, auxology, presence or not of DKA, severity of DKA, duration of symptoms and testing for SARS CoV-2 PCR or antibodies, where applicable. Collated data was analysed collectively and sub-analysis was undertaken for each centre. Children with type 2 diabetes, secondary diabetes and monogenic diabetes were excluded.

Statistical analysis

We used JASP (v 0.14.), JASP Team (2020), for our statistical analyses. Chi-squared significance tests were used to compare changing proportions and tests under the Poisson distribution were used to compare varying incidence rates over time. We constructed figures in Microsoft Excel for Mac (v 16.44).

Results

1. The demographic distribution of cases presenting with new onset diabetes, those in DKA and not in DKA, comparing 2019 to 2020 is illustrated in Table 1. There was a significant increase in the number of children presenting with DKA in 2020 when compared to 2019 (79 versus 49, $p<0.05$, $p=0.03$). There was also an increase in the number of children presenting with severe DKA in 2020 compared to 2019 (36 versus 16) (Figures 1 & 2). 25-32% of children who presented with new onset type 1 diabetes presented with DKA between 2016 to 2019, increasing to 44% in 2020.

2. The estimated incidence of new onset type 1 diabetes from January to July 2020 was similar to the previous years in 10PDUs. A clustering of cases in January, June, and July was noted in 2020 when compared to 2019. Seasonal variation of a peak in winter months and a trough in the summer months was not a feature of new-onset type 1 diabetes in 2020. There was a relative trough from mid-March to mid-April in 2020 (Figure 3).

3. Fluctuation from year to year in the total annual incidence of new-onset type 1 diabetes was noted when four years of data from the PDUs was collated (n=303 in 2016, 324 in 2017, 284 in 2018 and 312 in 2019, 332 in 2020) (Figure 4). Similarly, the incidence over a 7 month period from Jan-July showed a fluctuation from year to year (n=166 in 2016,190 in 2017, 174 in 2018, 150 in 2019, 178 in 2020) (Figure 5).

4. There was an unexplained apparent increase in incidence of new onset type 1 diabetes in 2 PDUs in January – July 2020 (15 cases in 2020, versus 4-9 cases from the same time period in the previous 4 years in PDU 1 and 12 cases in 2020, versus 5-9 cases from the same time period in the previous 4 years in PDU2).

5. There was no significant variation in ethnicity in children presenting with new-onset diabetes in 2020 when compared to 2019 in 9 units. Overall there was higher incidence of new-onset type 1 diabetes in White children. A higher proportion of Black children presented with type 1 diabetes in 2020 when compared to 2019 in two units (8 versus 4 in PDU1, 7 versus 3 in PDU2). A relative increase in the number of Asian children presenting with new-onset type 1 diabetes was noted in PDU3 (9 versus 5 in 2019).

6. The overall proportion of White children presenting in DKA was higher, but not significant: 55% (2019) versus 70% (2020).

7. Children younger than 5 years presenting with DKA constituted 10% of the total number of children presenting with DKA in 2019 increasing to 21% in 2020.

8. In 2019 35% of children had symptoms of less than 2 weeks (of which 43% were in DKA), 46% of children in 2020 presented with symptoms less than 2 weeks (of which 48% were in DKA).

9. Serology for COVID-19 antibodies was done in 11/178 patients and was found to be negative in all. 62 children had nasopharyngeal swabs for COVID-19, two children with new onset

type 1 diabetes tested positive.

10. Two children with new onset type 1 diabetes presented with severe DKA and shock and tested positive for SARS-CoV-2 on nasopharyngeal swabs, providing evidence of a link with diabetes and SARS-CoV-2. Both children needed admission in PICU. Both had good clinical outcomes.

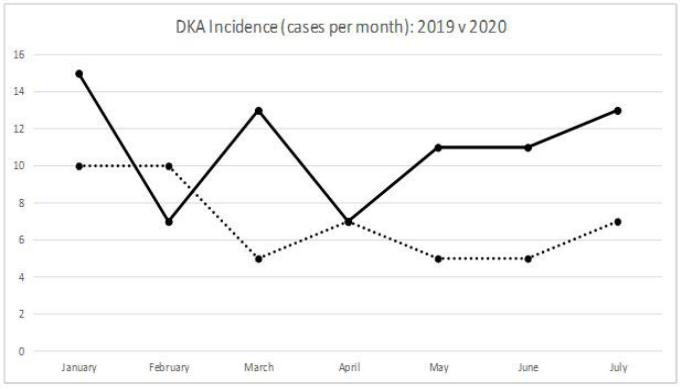

Figure 1: Incidence of DKA per month from January to July comparing 2019 and 2020 data. Abbreviations: DKA: Diabetes Ketoacidosis.

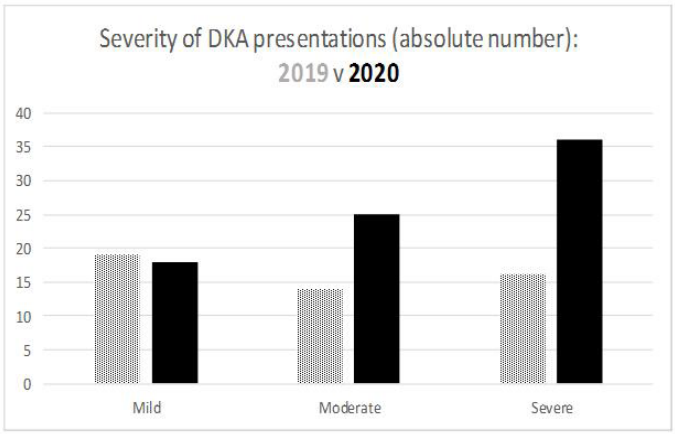

Figure 2: Severity of DKA presentations comparing 2019 to 2020. Abbreviations: DKA: Diabetes Ketoacidosis.

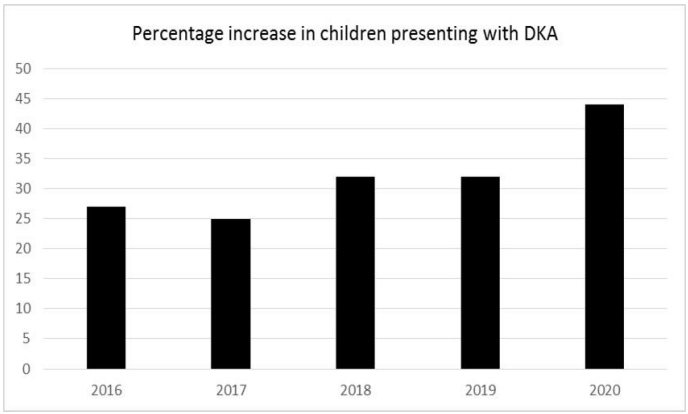

Figure 3: Percentage of children with new onset diabetes presenting in DKA over 5 years.

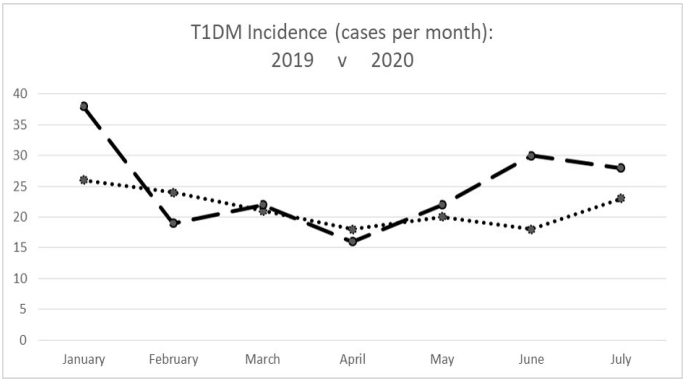

Figure 4: T1DM incidence cases per month from January to July for both 2019 and 2020 across all PDUs with clustering in January, June and July. Abbreviations: PDU: Paediatric Diabetes Unit; T1DM: Type 1 Diabetes Mellitus.

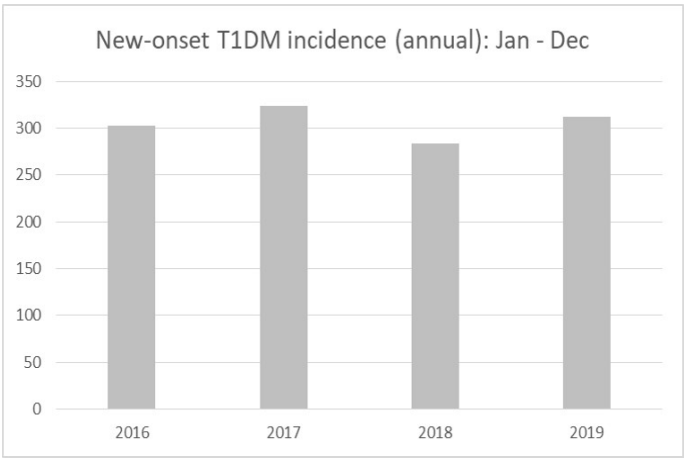

Figure 5: New onset T1DM annual incidence from 2016 to 2020 across all PDUs with fluctuations from year to year. Abbreviations: PDU: Paediatric Diabetes Unit; T1DM: Type 1 Diabetes Mellitus.

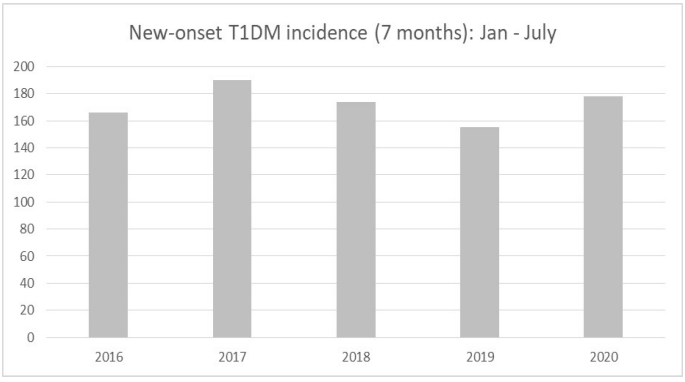

Figure 6: New onset T1DM incidence over a period of 7 months (January to July) from 2016 to 2020 across all PDUs with fluctuations from year to year.
Abbreviations: PDU: Paediatric Diabetes Unit; T1DM: Type 1 Diabetes Mellitus.

Table 1: Demographic distribution of cases presenting with new onset diabetes, those in DKA and not in DKA, comparing 2019 to 2020. Data are represented as N (%).

Abbreviations: DKA: Diabetes Ketoacidosis, PDU: Paediatric Diabetes Unit.

	Cases of new-onset diabetes in twelve PDUs (January to July)					
	2019			2020		
	All patients n = 150	Not in DKA (n = 101, 67.3%)	DKA (n = 49, 32.7%)	All patients n = 178	Not in DKA (n=99, 55.6%)	DKA (n = 79, 44.4%)
Age						
<5 years	21 (14)	16 (16)	5 (10)	33 (18)	17 (17)	16 (21)
5 - 11 years	61 (41)	42 (41)	19 (39)	70 (40)	46 (46)	24 (30)
12 - 17 years	68 (45)	43 (43)	25 (51)	75 (42)	36 (36)	39 (49)
Gender						
Male	80 (53)	56 (55)	24 (49)	89 (50)	42 (42)	47 (59)
Female	70 (47)	45 (45)	25 (51)	89 (50)	57 (58)	32 (41)
Duration of symptoms before presentation						
<2 weeks	52 (35)	31 (31)	21 (43)	81 (46)	43 (43)	38 (48)
2 weeks or greater	98 (65)	70 (69)	28 (57)	97 (54)	56 (57)	41 (52)
Ethnicity						
White	106 (71)	79 (78)	27 (55)	122 (68)	67 (67)	55 (70)
Black	17 (11)	7 (7)	10 (20)	27 (15)	15 (15)	12 (15)
Asian	10 (7)	5 (5)	5 (10)	14 (8)	8 (8)	6 (8)
Mixed	5 (3)	4 (4)	1 (2)	3 (2)	1 (1)	2 (3)
Other	12 (8)	6 (6)	6 (12)	12 (7)	8 (8)	4 (4)
DKA Severity (pH range)						
Mild (7.20 - 7.29)	-	-	19 (39)	-	-	18 (22)
Moderate (7.10 - 7.19)	-	-	14 (29)	-	-	25 (32)
Severe (<7.10)	-	-	16 (33)	-	-	36 (46)

Table 2: Absolute numbers of new onset T1DM cases across the 12 PDUs over a period of 7 months (2020) and corresponding number of DKA cases, with population covered by each PDU.

Abbreviations: DKA: Diabetes Ketoacidosis; PDU: Paediatric Diabetes Unit; T1DM: Type 1 Diabetes Mellitus.

PDU	1	2	3	4	5	6
Total Paediatric Population	180,700	138,300	188,657	150,000	135,000	132,089
New-onset type 1 diabetes cases	16	12	24	25	13	15
DKA cases	5	5	12	12	6	6
PDU	7	8	9	10	11	12
Total Population	124,672	111,000	109,000	89,958	78,500	78,400
New-onset type 1 diabetes cases	16	9	14	12	10	13
DKA cases	8	6	3	7	3	6

Discussion

I. Incidence and severity of DKA in 2020

The major finding of our study was a high number of children presenting with DKA at diagnosis in 2020. Studies from Europe, Australia and UK also reported that the frequency of severe diabetic ketoacidosis was significantly higher in the pandemic period compared to previous years [6-8]. Studies have proposed that COVID -19 related fear of attending ED was the reason for the incidence and severity of DKA in 2020 [2,3].

Results from our study showed that 35% of children had type 1 diabetes symptoms for less than 2 weeks (of which 43% were in DKA) in 2019. In comparison, 46% of children in 2020 presented with symptoms less than 2 weeks (of which 48% were in DKA). The short period of type 1 diabetes symptoms before presenting in DKA in 2020 does not suggest a delay in diagnosis.

Historically, delay in diagnosis of paediatric diabetes resulting in DKA has been a cause for concern before the onset of the pandemic. DKA incidence figures vary from 25% to 70% as reported from Europe and USA [9,10]. The causes for DKA are reported to be lack of parental and clinician awareness and de-

lay in referral whilst attempting to confirm the diagnosis by undertaking further diagnostic tests [10]. Children under 5 years can present with nonspecific symptoms which can delay recognition of type1 diabetes (10% of children in our study presented in DKA in 2019 increasing to 21% in 2020) Despite awareness campaigns, children with new-onset pediatric diabetes still presented in DKA in the pre pandemic period.

We need quantitative studies with objective documented evidence of delay due to COVID -19 related fear of attending ED to provide evidence and eliminate recall bias from the health professional. It will be important to understand parents' decision-making motives and reasoning in bringing their child to the hospital [11].

There has been speculation that the virus itself may trigger the development of ketoacidosis via direct damage to pancreatic beta cells, based on observations that other coronaviruses bind to ACE2 receptors expressed by these cells [12]. Studies from adult medicine have proposed a possible bidirectional relationship with COVID-19 [13]. Furthermore, there are precedents for a viral cause of diabetes, including other coronaviruses that bind to ACE2 receptors [14].

The short period of symptoms of type 1 diabetes at presentation during the study period and the severity of DKA raises the possibility that infection with SARS–CoV–2 may have been a trigger resulting in a rapid loss of β-cells contributing to the rise in incidence and severity of DKA also accelerating the development of new-onset diabetes. This association could not be ascertained due to limited number of children tested during the study period for COVID-19 antibodies. COVID-19 serology was done in only 11/178 children as the surge of children with new onset type 1 diabetes was noticed in July 2020.

The overall mean prevalence of DKA in our study was higher in White chldren compared to children from ethnic minority. This is in contrast to most countries and previous worldwide studies in which ethnic minority status was associated with a higher prevalence of DKA at diagnosis in the pre pandemic period.

II. Paediatric diabetes research in context

The current prevailing paradigm on the aetiology of new-onset type 1 diabetes hypothesizes that environmentally triggered autoimmune destruction of pancreatic beta cells occurs against the background of genetic risk [15]. Viral etiology of new-onset type 1 diabetes has been studied extensively but a definite causation has not been proved. Enterovirus has been the main virus of interest [16]. The picture is complicated as the period of time between a viral infection and the initiation of autoimmunity varies making the occurrence of a critical infectious event extremely hard to detect [17]. A case report from Germany describes an acute onset of type 1 diabetes after infection with SARS-CoV-2 in a 19-year-old boy [18]. A study reported an increase in the number of new type 1 diabetes cases in children compared with a typical year and proposed that SARS-CoV-2 is linked with the increased incidence although causality could not be established [1]. A third study from Germany reported that the rate of new-onset paediatric type 1 diabetes observed across Germany from mid-March to mid-May 2020 did not differ significantly from predicted rates based on data collected over the last decade [19]. Stratifying by age and sex, we found no significant differences between observed and estimated incidence of new-onset type 1 diabetes in 2020 in 10 PDUs when compared to the previous four years. We noted an apparent increase in incidence in 2020 from two PDUs. Both these units were from inner city localities with a high Black population. Environmental factors specific to these geographical areas could have contributed to the increased incidence. Both these factors should be interpreted with caution. The observed patterns may be attributable to random variation or clustering of cases in a high incidence year. An apparent increased incidence was also noted in Asian children in 2020 from PDU3 when compared to the previous year. It is difficult to conclude based on data from a small time period. The incidence of new-onset type 1 diabetes in Black and Asian population should be observed over a period of time to understand the trend.

Seasonal variation in incidence of new-onset type 1 diabetes manifested by a peak in winter and a trough in the summer months has been reported from several [20,21] but not all countries [22]. The incidence of new-onset type 1 diabetes started to increase steadily from May 2020 with a peak in June and July, the expected trough in the summer months did not happen. The overall incidence of paediatric diabetes is increasing, but total numbers fluctuate over time as shown by the annual incidence data of new onset type 1 diabetes from the PDUs. Short term variation in incidence are a feature of diabetes epidemiology which complicates interpretation of epidemics [23]. Since autoimmunity and progressive beta cell destruction typically start long before the clinical diagnosis of type 1 diabetes, the periodicity in diagnosis could be indicative of cycles of infectious disease that accelerate the diagnosis rather than initiate the disease [24].

III. **Establishing causation**

The definitive test for diagnosis of COVID-19 is detection of SARS-CoV-2 RNA by real-time reverse transcription-PCR (RT-PCR) which has sensitivity reported to vary between 58% to 95% with a specificity of 97.7% [25]. The technique and the diagnostic testing window are perhaps the most important factors impacting test sensitivity [26]. False negatives are operator dependant and are also influenced by low viral loads in the early and late stages of infection [27]. 62 children had nasopharyngeal swabs for COVID-19, two children with new onset type 1 diabetes tested positive. Both presented with severe DKA and cerebral edema. It is likely that the infection with SARS-CoV-2 resulted in severe DKA in both children and accelerated the diagnosis of new onset type 1 diabetes. Both had good clinical outcomes. Qualitative studies with a timeline for individual patients plotting the course of events prior to diagnosis with new onset type 1 diabetes will give further corroborative evidence.

Serology includes IgG and IgM antibody to SARS-CoV-2. This does not have a role in acute illness but will show past exposure to COVID-19.

T cell immunity can be the only evidence of infection with COVID- 19 in the absence of antibodies. A recent study showed that eleven per cent of 76 health care workers with laboratory confirmed SARS-CoV-2 infection lacked antibodies to COVID-19 but had T cells reactive with other SARS-CoV-2 antigens. Discordant T cell and antibody responses could mean that patients with previous infection with SARS-CoV-2 can be missed if tested only for humoral immunity [28].

Proving or disproving causation is therefore difficult given the challenges of testing for SARS-CoV-2. Furthermore association with SARS-CoV-2 in children who test positive by the above methods may not indicate causation.

Conclusions

Our study provides an overview of the incidence and the severity of DKA in children with new-onset paediatric diabetes in the pandemic and the challenges in finding or disproving an association with SARS-CoV-2. The major findings were an increase in the number of children presenting with DKA at diagnosis in 2020 compared to the previous four years. Delay in diagnosis was a not a significant factor in decompensation to DKA.

Our study did not provide evidence that the COVID-19 pandemic is leading to a dramatic increase in incidence of paediatric type 1 diabetes. However, there was an apparent increase in incidence in two PDUs. Whether this was a true increased incidence or isolated clusters in a specific geographical area in a high incidence year is unclear. The finding of an apparent increase in type 1 diabetes in children of ethnic minority in 2020 needs to be monitored over time as the demographical characteristics of the geographical area may have contributed.

Association with SARS-CoV-2 could not be ascertained from the datasets used in this study due to the limited number of children tested for COVID-19 serology as the study was done in the first wave of the pandemic. Review of the sensitivity of the tests used for COVID -19 showed that proving causation can be challenging.

A mixture of qualitative and quantitative aspects in this study indicates that there is a likely link between COVID-19 and diabetic ketoacidosis in children presenting with type 1 diabetes in the pandemic.

In light of the above findings, the relationship between diabetes and SARS-CoV-2 should trigger more research including in vitro studies to understand the specific mechanisms of the virus such as its possible tropism for the pancreatic β-cells. We recommend universal COVID 19 serology testing in children with new-onset diabetes in the pandemic. It is important to emphasise early recognition and prevention of DKA in children with new-onset paediatric diabetes given the high incidence in the pandemic.

Strengths and limitations

Our study collected data from 12 paediatric diabetes units which is the largest dataset in the UK to date. Each centre has a defined geographical area and population providing a near 100% of new-onset diabetes from that area being picked up. Population movement can still cause an occasional patient with new-onset diabetes to be missed, similarly a new-onset diabetes from another area can be picked up; however, population movement during the pandemic was restricted. Small numbers being tested for COVID-19 serology was a limitation in our study. We did not include children previously known to have diabetes who presented to ED during the pandemic.

Declarations

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Conflicts of interest/Competing interests: None of the authors have any conflicting interests to disclose

Availability of data and material: All data and materials are available upon request

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