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SARS-CoV-2 infection in hospitalized children with type 1 and type 2 diabetes

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ABSTRACT

Context: While diabetes is a risk factor for severe illness from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults, there is conflicting data surrounding the relationship between the virus and diabetic disease process in children.
Objective: This case series aims to illustrate an increase in the incidence of types 1 and 2 diabetes mellitus (T1DM, T2DM) between April – November 2020 at a large tertiary care children's hospital and examine the characteristics and adverse outcomes in these children. In addition, two children with significant complications from coronavirus disease 2019 (COVID-19) and diabetes are highlighted.
Methods: Hospitalized children with T1DM or T2DM and SARS-CoV-2 infection were identified, and electronic medical records were reviewed.
Results: We observed a 16.3% increased rate of new-onset T1DM and 205.3% increased rate of new-onset insulin-dependent T2DM between April and November 2020 when compared to the same observational time frame in 2019. Among children with new-onset T1DM, 56.9% presented with DKA in 2019 and 47.1% in 2018 compared to 64.3% in 2020, which was higher than the national average. Twenty-eight children were diagnosed with COVID-19 and diabetes during this time. The 2 described cases with significant complications from COVID-19 and DKA required large doses of intravenous insulin over a prolonged duration.
Conclusion: This study highlights that the COVID-19 pandemic might have led to an increased rate of new-onset T1DM, T2DM, and DKA in children and adolescents compared to a similar time frame in the prior 2 years. The clinical phenotypes and outcomes in children with diabetes to COVID-19 infection may be distinct and therefore, future pediatric specific studies are needed to define the role of SARS-CoV-2.

Introduction

As the coronavirus disease 2019 (COVID-19) pandemic continues affecting > 188 countries/territories around the globe, new associations between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] and other pediatric disease processes are being reported. The diabetogenic effect of the novel coronavirus is being debated, both with its potential effect on precipitating glycemic failure in children as well as its ability to worsen metabolic complications of Type 1 diabetes mellitus (T1DM), including diabetic ketoacidosis (DKA), which is characterized by hyperglycemia, ketosis, and metabolic acidosis. Several reports suggest that this effect may be beyond the well-studied triggers from other viral illnesses [2–5]. A study from Germany suggested an increase in DKA at diabetes diagnosis among patients with COVID-19 [6]. However, other reports fail to demonstrate this association [7,8]. The role of SARS-CoV-2 on type 2 diabetes (T2DM) incidence in children and complications in children with known T2DM has also not been well described. This study aims to illustrate the increased occurrence of new-onset T1DM and T2DM between April to November 2020, compared to the same observational time frames in the previous 2 years, at a tertiary care children's hospital in the state of Alabama with a large referral base. We also describe the characteristics and outcomes of children

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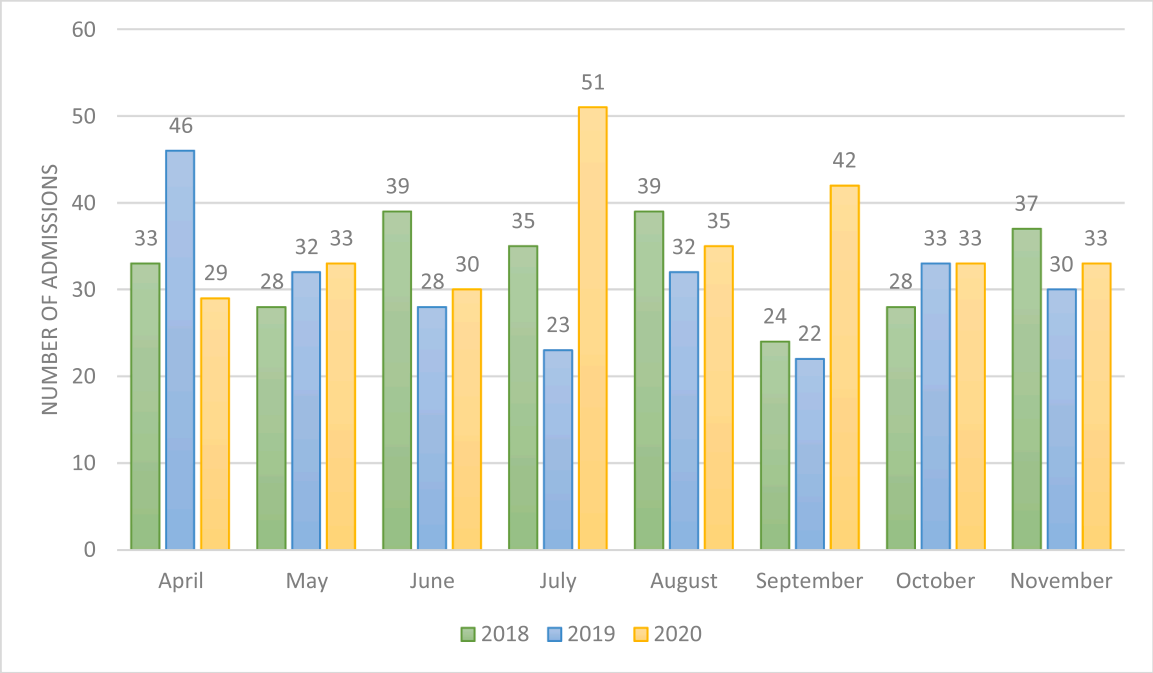

Fig. 1. Hospitalized Children with New-Onset Type 1 Diabetes from April to November 2018–2020. Bar diagram showing the number of hospitalized children with new-onset T1DM between the months of April to November in 2018, 2019 and 2020. T1DM = Type 1 diabetes mellitus.

admitted with T1DM or T2DM during the months of April to November 2020 with SARS-CoV-2 infection in order to identify possible factors underlying this trend in increased occurrence and highlight two key cases of T1DM and T2DM whose clinical courses were complicated by COVID-19 to illustrate differences in management strategies.

Materials and methods

With a hospital-wide policy of screening all admissions for COVID-19 instituted on April 27, 2020, hospitalized children with SARS-CoV-2 infection were identified and enrolled into a natural history study approved by the Institutional Review Board (IRB) for Human Use, and informed consent was obtained. Nasopharyngeal (NP) samples were analyzed by reverse transcription polymerase chain reaction (RT-PCR), and viral loads were determined by generating a standard curve based on dilutions of known SARS-CoV-2 genomic RNA obtained from the World Reference Center for Emerging Viruses and Arboviruses, with a limit of detection between 600 and 800 copies/mL [9]. The International Classification of Diseases tenth revision – Clinical Modification (ICD-10-CM) diagnosis codes E10.9, E10.10, E10.65, E11.0, E11.10, E11.65 and E11.9 were used to identify all potentially eligible patients with a physician-ascertained diagnosis of T1DM or T2DM from April-November for the years 2018–2020. This was cross referenced with an ongoing diabetes data registry maintained by the division of pediatric endocrinology at Children's of Alabama to ensure accuracy of the data collected. All children with new onset T1DM were hospitalized for inpatient diabetes education. Children and adolescents with new onset T2DM were hospitalized if they have a hemoglobin A1C (HbA1C) of 8.5% or more for management with insulin therapy. Moreover, all children with diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS) were also admitted. The categorizations of DKA as mild, moderate, and severe were based on pH $\geq$ 7.2 and/or bicarbonate $<$ 15 mmol/L, pH 7.1–7.2 and/or bicarbonate $<$ 10 mmol/L, and pH $\leq$ 7.1 and/or bicarbonate $<$ 5 mmol/L, respectively. The data on clinical characteristics and the case reports were manually reviewed and collated.

Results

Fig. 1 illustrates the number of admissions for new onset T1DM from April to November 2020 at Children's of Alabama. For T1DM, an overall annual trend in increased incidence is seen between April – November 2020 with 286 children admitted with new-onset T1DM when compared to 246 children in 2019, a 16.3% increase. This contrasts with the same observational time frame in the year prior, during which a 6.5% yearly decrease was seen from 2018 to 2019. A considerable increase in the number of children with T1DM who presented with DKA during the period between April and November 2020 was seen, representing 64.3% compared to 56.9% in 2019 and 47.1% in 2018. A more significant increase in T2DM (205.3%) was seen from April - November 2020 with 290 children hospitalized with new-onset T2DM, compared to 95 children during the same time frame in 2019 and 88 children in 2018. Of the children admitted with new-onset T2DM, 59.3% presented with DKA, compared to 4.2% in 2019 and 5.7% in 2018. Fig. 1 represents the trends of new-onset T1DM admissions by month, comparing annual trends from 2018 to 2020. The demographic, clinical, and laboratory characteristics of all patients with either T1DM or T2DM and SARS-CoV-2 infection are shown in Table 1.

Twenty-eight children were hospitalized with diabetes and COVID-19 between April – November 2020. Of the children admitted with a T1DM diagnosis, 21 tested positive for SARS-CoV-2 RNA by RT-PCR of NP swabs. SARS-CoV-2 viral loads for these children ranged from 1.46 x 10^3 to 1.07 x 10^8 copies/mL. The majority (16/18 or 89%) of these children did not have significant pulmonary disease regardless of the severity of their DKA, nor did higher viral loads predict or correlate with the severity of DKA. Tables 2 and 3 represent the demographic, clinical, and laboratory characteristics of patients with new-onset or preexisting T1DM and SARS-CoV-2 infection. The majority (89% and 75%, respectively) of children with new-onset or preexisting T1DM and COVID-19 presented with DKA (Tables 2 and 3). Of these, one child had severe DKA and COVID-19, and his management has been elaborated below.

Fig. 2 depicts the number of admissions for new-onset T2DM from April to November 2020 at Children's of Alabama. Seven of the 28 children with COVID-19 and a diagnosis of diabetes had T2DM (25%).

Table 1
Demographic, Clinical and Laboratory Characteristics of Children Infected with SARS-CoV-2 Presenting with Diabetes/Diabetic Ketoacidosis.

	New-onset diabetes		Known diabetes		All patients (n = 28)
	Type 1 (n = 9)	Type 2 (n = 1)	Type 1 (n = 12)	Type 2 (n = 6)	
Mean age (years)	10.5	15	12.4	16.5	12.8
Gender					
Female	7	0	6	5	18 (64%)
Male	2	1	6	1	10 (36%)
Race/ethnicity					
White	5	0	3	2	10 (36%)
Black	4	1	7	4	16 (57%)
Hispanic	0	0	2	0	2 (7%)
Mean body mass index (kg/m^2)	17.7	37.5	22.4	43.6	27.0
Mean body mass index z score	−0.74	+2.58	+1.05	+2.45	+0.88
Pancreatic autoantibodies					
Glutamic acid decarboxylase antibody	7	–	10	–	17/21 (80.9%)
Islet cell antibody	1	–	3	–	4/18 (22.2%)
Insulinoma antigen 2 antibody	1	–	3	–	3/8 (37.5%)
Zinc transporter 8 antibody	1	–	3	–	4/9 (44.4%)
Mean duration of diabetes (years)	–	–	3.8	3	3.5
Mean hemoglobin A1C (%) at presentation	12.9	11.7	11.6	8.5	11.3
Mean SARS-CoV-2 viral load (copies/mL)	1.92x10^7	3.82x10^7	2.97x10^6	2.73x10^6	8.87×10^6
Diabetic ketoacidosis					
None	1	0	3	6	10 (36%)
Mild (pH ≥ 7.2, bicarbonate < 15 mmol/L)	4	0	4	0	8/18 (44%)
Moderate (pH 7.1–7.2, bicarbonate < 10 mmol/L)	2	1	2	0	5/18 (28%)
Severe (pH ≤ 7.1, bicarbonate < 5 mmol/L)	2	0	3	0	5/18 (28%)
Other complications					
Pneumonia	0	1	1	1	3 (11%)
Acute kidney injury	0	0	1	1	2 (7%)
Transaminitis	0	1	0	1	2 (7%)
Rhabdomyolysis	0	0	0	1	1 (4%)

Table 4 represents the demographic, clinical, and laboratory characteristics of children with T2DM and SARS-CoV-2 infection. Their viral loads ranged from 8.28 x 10^2 to 3.82 x 10^7 copies/mL. The levels of SARS-CoV-2 viral load between children with T1DM and T2DM did not differ significantly, nor did it differ between children with new-onset diabetes and those with pre-existing diabetes. Four of the children with T2DM had a recent HbA1C of ≥ 8.5% (69.4 mmol/mol), meeting the American Diabetes Association 2020 (ADA) recommendations for insulin initiation. One child with T2DM and COVID-19 had a presentation complicated by severe mixed DKA and HHS, and his management has been elaborated below.

Case A: T1DM with DKA, COVID-19 and complications

An 8-year-old White male with established T1DM diagnosed in 2014 presented to his local emergency department with 3 days of emesis and labored respirations. Laboratory evaluation revealed a serum glucose 442 mg/dL, pH 6.77, and bicarbonate 2.2 mmol/L, consistent with a diagnosis of severe DKA. He received intravenous fluids for volume repletion and was started on a continuous insulin infusion at 0.15 unit/kg/hour. He remained significantly acidotic with pH values ranging between 6.7 and 6.9 for the next 6 h, requiring a bicarbonate infusion for the worsening mixed acidosis. His anion gap corrected 12 h after initiation of insulin therapy.

Shortly after arrival to the emergency department, the patient became hypoxic and tested positive for SARS-CoV-2 by RT-PCR. Chest x-ray showed bilateral infiltrates, and his oxygen requirement quickly escalated requiring intubation. The patient was started on remdesivir 5 mg/kg intravenously (IV) followed by 2.5 mg/kg IV daily and dexamethasone 0.15 mg/kg IV daily for his severe COVID-19. Initial echocardiogram revealed an ejection fraction of 42%, which improved to 50% two days later. He then developed pulmonary edema and worsening renal dysfunction refractory to diuretics, and he was transferred to our institution on hospital day 3 for dialysis.

Vital signs upon transfer included a temperature 36.1 °C, heart rate 139 beats per minute, respiratory rate 22 breaths per minute, blood pressure 96/51 mmHg, and oxygen saturation 96% on mechanical ventilation. Physical examination was notable for anasarca, and he soon progressed to hemodynamic instability requiring 3 vasopressors. He was started on continuous renal replacement therapy (CRRT) the following day for acute renal failure, and remdesivir was discontinued due to decreased renal clearance. With severe COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), and the potential for poor subcutaneous absorption in the presence of systemic inflammation, the patient was continued on a prolonged insulin drip for 16 days for management of his hyperglycemia. CRRT was discontinued after 10 days, and his renal function recovered. He was extubated 13 days after transfer to our hospital and was subsequently weaned to room air 9 days later. The patient was hospitalized for a total of 36 days, and SARS-CoV-2 RNA remained detectable from his upper respiratory tract throughout his hospitalization.

Case B: T2DM with DKA, COVID-19 and complications

A 15-year-old Black male with a new diagnosis of T2DM presented with progressive myalgia, fatigue, several days of polydipsia, and altered mental status to the emergency room. He had a body weight of 90 kg and BMI of 37.5 kg/m2. He was hypertensive (168/98 mmHg), tachycardic to 140 beats per minute, tachypneic with a respiratory rate > 35 breaths per minute, and hypoxic (oxygen saturation, 88%) upon presentation. Laboratory evaluation revealed a serum glucose of 2238 mg/dL, pH 7.18, bicarbonate 9 mmol/L, serum osmolarity of 401 mOsm/L – consistent with a diagnosis of mixed DKA and HHS. The patient had concomitant lactic acidosis, severe dehydration with a BUN

Table 2
Demographic, Clinical and Laboratory Characteristics of Patients with New-Onset T1DM and SARS-CoV-2 Infection.

Variable	Case 1*	2	3	4	5**	6	7	8	9
Age (years)	12	11	13	14	12	8	13	3	9
Gender	Male	Female	Male	Female	Female	Female	Female	Female	Female
Race/ethnicity	White	Black	White	Black	Black	Black	White	White	White
BMI (kg/m^2)	18.6	28.4	18.2	16.8	16.9	11.9	15.6	15.2	12
BMI z score	+ 0.10	+ 2.10	−0.39	−1.21	−0.68	−3.99	−1.57	−0.3	−3.9
Comorbidities	Asthma	Obesity	None	None	Vitamin D deficiency	Asthma	None	H3F3A mutation, developmental delay, epilepsy, dysphagia	None
Reason for admission	NOD	NOD, DKA	NOD, DKA	NOD, DKA	NOD, DKA	NOD, DKA	NOD, DKA	NOD, DKA	NOD, DKA
Glutamic acid decarboxylase antibody	–	+	+	+	–	+	+	+	+
Islet cell antibody	–	–	–	–	–	–	–	+	–
Other autoantibodies	Negative IA-2 and ZnTr8	Negative IA-2 and ZnTr8	NA	Positive IA-2 and ZnTr8	Negative IA-2 and ZnTr8	NA	NA	Negative ZnTr8	NA
Hemoglobin A1C (%) at presentation	>14.0	13.2	>14.0	10.6	>14.0	>14.0	>14.0	7.9	>14.0
SARS-CoV-2 viral load (copies/mL)	1.24x10^5	4.41x10^4	NA	9.28x10^5	NA	1.07x10^8	1.67x10^7	9.47x10^6	1.46x10^3
Severity of diabetic ketoacidosis	None	Mild	Mild	Severe	Moderate	Moderate	Mild	Mild	Severe
Initial venous blood gas pH	7.36	7.27	7.27	7.01	7.14	7.11	7.30	7.22	6.85
Serum bicarbonate (mmol/L)	21	14	13	6	<5	6	13	10	<5
Serum glucose (mg/dL)	372	216	290	642	367	397	427	1134	482
Urine ketones	2+	3+	2+	2+	4+	2+	3+	2+	4+

*Case 1 was negative for autoantibodies that are usually present in Type 1 diabetes mellitus (T1DM). Nevertheless, a diagnosis of antibody-negative T1DM was made given the normal BMI, absence of acanthosis nigricans and a strong family history of T1DM in multiple first-degree relatives, including mother and maternal grandfather.
**Case 5 was also negative for autoantibodies that are usually present in T1DM. A diagnosis of antibody-negative T1DM was made given normal BMI, lack of acanthosis nigricans and a strong family history of autoimmunity.
Abbreviations: BMI = Body mass index; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; T1DM = Type 1 diabetes mellitus; NA = Not available; IA-2 = Insulinoma antigen 2 antibodies; ZnTr8 = Zinc transporter 8 antibodies; NOD = New-onset diabetes; DKA = Diabetic ketoacidosis.

of 42 mg/dL and a serum creatinine of 2.9 mg/dL. He received 2 L of Lactated Ringer's solution and IV mannitol. Subsequently, he was intubated due to progressively worsening mental status. He remained critically ill, developed hypovolemic shock requiring further aggressive fluid resuscitation (an additional 110 mL/kg within the first six hours of admission), and initiation of IV vasopressin and norepinephrine for pressor support. The patient was started on 0.1 U/kg/hr of insulin therapy, which was gradually increased to 0.2 U/kg/hr by 24 h due to hyperglycemia. With elevated erythrocyte sedimentation rates and ferritin levels, he also developed macrophage activation syndrome (MAS), for which he was treated with anakinra, an interleukin-1 receptor antagonist. He required CRRT for progressive renal failure and anuria, and due to persistent hyperglycemia, the patient required 2.7 U/kg/hr of IV insulin in addition to 1 U/kg/dose Lantus q24h. He was transitioned off the insulin drip to subcutaneous Lantus at a dose of 2 U/kg/day seventeen days after his admission.

Discussion

Through this case series, we describe 28 pediatric patients within an 8-month period with concurrent SARS-CoV-2 infection and metabolic complications from type 1 or type 2 diabetes. It is important to recognize that patients with uncontrolled T1DM or T2DM are at risk for severe illness from SARS-CoV-2 infection. Our report shows a potential association between SARS-CoV-2 and poor glycemic control resulting in DKA, and this is worrisome because poor glycemic control is fairly common in the pediatric diabetes population, with < 50% of children achieving HbA1C ≤ 7.5% (58.5 mmol/mol) across the world [10]. Furthermore, the two highlighted cases suggest that management of hyperglycemia may be difficult [11] during severe illness from SARS-CoV-2 infection. Such severity, although less commonly seen in children, has been reported throughout the U.S. and Canada, with higher rates of severe DKA seen during the COVID-19 pandemic [12,13].

Increased rates of new-onset diabetes: Limited data to date reports an increase in the number of new-onset T1DM and DKA cases in the United Kingdom [14] and Germany [6], but a decrease was seen in Italy [7,15] and India [8] during the early period of the pandemic. With increased rates of new-onset T1DM and T2DM pediatric admissions in 2020 at our institution, these findings are consistent with studies suggesting an increased occurrence of new-onset T1DM that may be precipitated by COVID-19 [16]. Even though there have been reports on COVID-19 and T1DM in children [11], the data on T2DM in children have been sparse. Interestingly, we found an increase in the number of admissions for new-onset diabetes, particularly T2DM (205.3% increase), during the months of April through November 2020, compared to previous years, at our institution. This is significantly increased from the trends reported by SEARCH for Diabetes in Youth Study from 2002 to 2015, during which time the annual percentage changes in T1DM and T2DM incidences were 1.9% per year and 4.8% per year, respectively [17]. Globally, the average increase in T1DM incidence is 3–4% per year [18]. We also found an increased incidence of DKA in our new-onset T1DM population when compared to overall nationwide averages in

Table 3
Demographic, Clinical and Laboratory Characteristics of Patients with Preexisting T1DM and SARS-CoV-2 Infection.

Variable	Case 1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	17	10	15	17	15	5	13	16	13	15	5	8
Gender	Female	Female	Male	Female	Male	Male	Female	Male	Female	Female	Male	Male
Race/ethnicity	Black	Hispanic	Black	Black	Hispanic	Black	Black	Black	Black	White	White	White
BMI (kg/m^2)	32.8	22.8	24.1	23.1	25.7	15.7	20.4	24.1	22.9	26.3	17.1	15.5
BMI z score	+1.9	+1.82	+1.01	+0.6	+1.80	+0.23	+0.55	+1.01	+1.22	+1.34	+1.16	−0.05
Comorbidities	Obesity, depression, anxiety	None	Overweight	None	Overweight	Microalbuminuria	None	Bipolar disorder, ADHD	ADHD, depression	PCOS, depression	Dehydration	None
Reason for admission	Diabetes education	DKA	DKA	DKA	DKA	DKA	DKA	DKA	DKA	Suicidal ideation	IV rehydration	DKA
Duration of Type 1 diabetes mellitus	<1 year	1 year	3 years	8 years	4 years	4 years	4 years	4 years	4 years	4 years	4 years	6 years
Glutamic acid decarboxylase antibody	+	–	+	+	+	+	+	+	+	+	–	+
Islet cell antibody	–	–	–	+	–	+	–	–	NA	NA	+	NA
Other autoantibodies	NA	NA	NA	NA	NA	IA-2NA and positive ZnTr8	Positive IA-2 and ZnTr8	Positive IA-2 ZnTr8 NA	Positive IA-2 and ZnTr8	NA	NA	IA-2NA and negative ZnTr8
Hemoglobin A1C (%) in 2019	–	9	13.7	7.7	>14.0	12.7	>14.0	>14	8.2	12.4	9.5	>14.0
Hemoglobin A1C (%) at presentation in 2020	8.8	10.1	>14.0	8.2	>14.0	13.1	>14.0	>14.0	7.6	11.1	9.7	>14.0
SARS-CoV-2 viral load (copies/mL)	$1.89x10^3$	$1.59x10^7$	$5.48x10^2$	$9.67x10^2$	$1.46x10^3$	$4.65x10^4$	$4.10x10^3$	$3.74x10^6$	$1.51x10^7$	$1.09x10^4$	$2.83x10^5$	$5.54x10^5$
Severity of diabetic ketoacidosis	None	Mild	Severe	Mild	Moderate	Moderate	Mild	Mild	None	Severe	None	Severe
Initial venous blood gas pH	7.38	7.23	7.04	7.25	7.20	7.10	7.29	7.30	–	7.00	7.43	6.77
Serum bicarbonate (mmol/L)	20	8	6	11	14	14	16	11	–	<5	14	2.2
Serum glucose (mg/dL)	119	314	478	203	535	338	430	511	65	299	356	442
Urine ketones	NA	4+	3+	2+	3+	2+	1+	+	–	+	NA	3+

Abbreviations: BMI = Body mass index; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; NA = Not available; IA-2 = Insulinoma antigen 2 antibodies; ZnTr8 = Zinc transporter 8 antibodies; ADHD = attention deficit hyperactivity disorder; PCOS = polycystic ovarian syndrome; DKA = diabetic ketoacidosis.

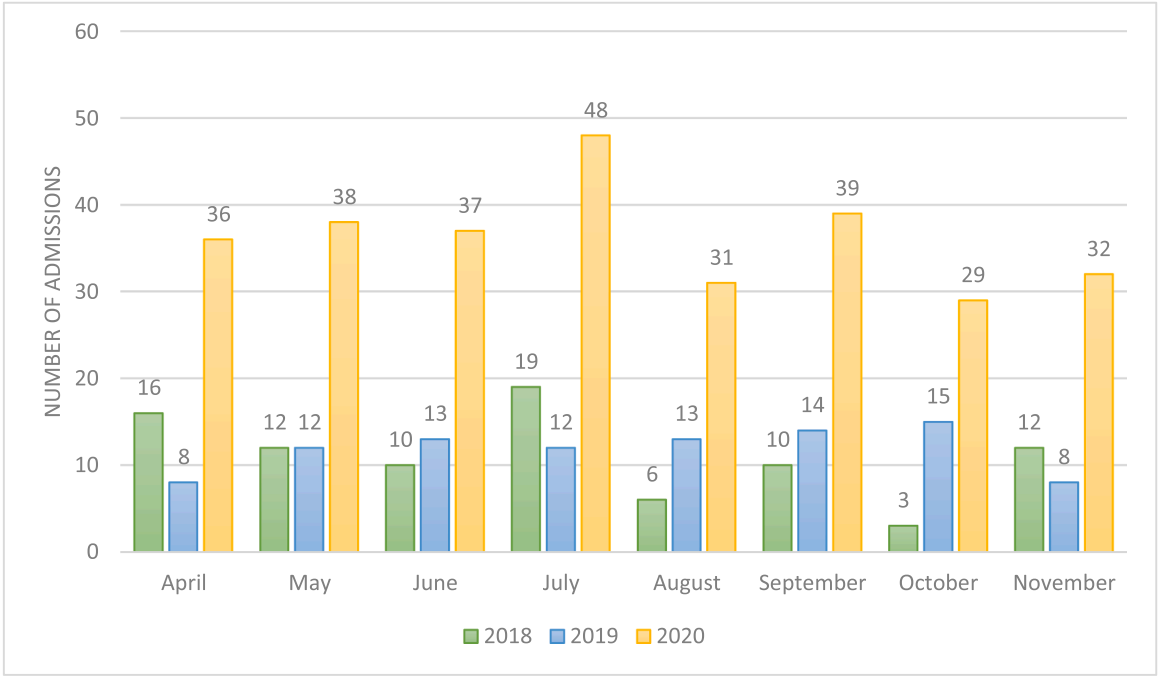

Fig. 2. Hospitalized Children with New-Onset Type 2 Diabetes from April to November 2018–2020. Bar diagram showing the number of hospitalized children with new-onset T2DM between the months of April to November in 2018, 2019 and 2020. T2DM = Type 2 diabetes mellitus.

new-onset diabetes, which average around 30% [19], which is in accordance with several other studies [6,12,13]. Our report also highlights the need for further investigation into the potential diabetogenic effect of COVID-19. There are several proposed mechanisms for new-onset diabetes during SARS-CoV-2 infection - whether the diabetes originated from the infection, or the infection triggered autoimmunity. The novel coronavirus enters host cells by binding to angiotensin-converting enzyme 2 (ACE2), a transmembrane glycoprotein with proteolytic activity that can be found expressed on many tissue cells, including pancreatic β-cells as well as exocrine pancreatic cells [20,21]. It has been shown that SARS-CoV-2 infects [22] and replicates in pancreatic cells, thereby altering pancreatic β-cell function directly and impairing insulin secretion [23–25]. In addition, the novel coronavirus could trigger autoimmunity. Thus, both autoantibody-negative and autoantibody-positive insulin-dependent diabetes can occur during a SARS-CoV-2 infection. In the case of T2DM, social distancing with indoor stay, increased time out of school, consumption of high-calorie foods, isolation with further reduction in exercise, worsening of obesogenic factors in a genetically predisposed population, and health disparities with delayed seeking of health care may have all contributed towards a higher incidence as the pandemic progressed [26].

T2DM and COVID-19: This manuscript adds to the knowledge regarding the characteristics of T2DM in children with COVID-19 infection and demonstrate how this viral infection may worsen the already dysregulated glucose metabolism [27] with 3 of 7 children presenting with an increased insulin requirement.

When the children with T1DM are compared to those with T2DM, the elevated BMI in the T2DM group is apparent. Obesity is a well-established risk factor for T2DM. A variety of social and environmental risk factors had led to increased BMI during the observational time frame – lack of school, increased sedentary lifestyle, chronic stress and increased caloric intake, reduced availability and access to sports and activities that would have been otherwise expected in summer months, increased social isolation and food insecurity. A recent data analysis from the Centers for Disease Control showed that the rate of BMI increase approximately doubled during the pandemic compared to a prepandemic period among children and adolescents [28].

DKA and COVID-19: Eighteen (64.3%) of the 28 children presented in DKA of varying severity, 10 (55.6%) of whom were Black. This is perhaps reflective of health disparities, as they are becoming increasingly recognized [29]. The 12 children with pre-existing T1DM had uncontrolled diabetes with markedly elevated HbA1C before hospital admission. This observation is analogous to the reports from adults with diabetes in whom poor glycemic control is a risk factor for adverse metabolic outcomes [30]. A similar observation was also noted in the preliminary reports from the T1D Exchange [11].

The limitations of our study include a small sample size at a single center. We are also unable to capture the number of known persons with diabetes with COVID-19 who did not require hospitalization. The serum antibodies targeted against SARS-CoV-2 were not evaluated for any of these patients and in the overall group of hospitalized children with diabetes to identify a recent/past infection. Thus, we are unable to establish the association between recent SARS-CoV-2 infection and increased cases of new-onset diabetes in our patient population. However, with PCR positivity upon admission, it is likely that these children were acutely infected with SARS-CoV-2. Our review of data was also relatively limited, comparing 2020 to a similar time frame in the prior 2 years. Therefore, larger prospective studies are needed to better delineate the change in trends over time and understand the longitudinal impact on overall incidence.

In conclusion, this report highlights the importance of testing all children presenting with new-onset diabetes or DKA for COVID-19. In addition, this report also raises the need for further research into the relationship between SARS-CoV-2 and diabetes and why some children

Table 4
Demographic, Clinical and Laboratory Characteristics of Patients with T2DM and SARS-CoV-2 Infection.

Variable	Case 1	2	3	4	5	6	7
Age (years)	16	19	16	13	15	19	16
Gender	Male	Female	Female	Female	Male	Female	Female
Race/ethnicity	Black	White	Black	Black	Black	White	Black
BMI (kg/m^2)	47.6	29.1	46.0	42.6	37.5	43.0	53
BMI z score	+3.02	+1.44	+2.57	+2.68	+2.58	+2.28	+2.72
Comorbidities	HTN, obesity	Medulloblastoma, epilepsy, OSA, hypothyroidism, PCOS, gastroparesis	Asthma, obesity, HTN	Seasonal allergies, obesity	None	Shunted hydrocephalus	Obesity, fatty liver
Reason for admission	Severe rhabdomyolysis	Dehydration	Hypoxia	New insulin requirement	New insulin requirement, DKA, HHS, heart failure	New insulin requirement	Tremors – concern for new seizures
Duration of Type 2 diabetes mellitus	3 years	4 years	4 years	2 years	<1 year	2 years	<1 year
Hemoglobin A1C (%) in 2019	6.6	6.0	>14	6.1	NA	7.2	NA
Hemoglobin A1C (%) at presentation in 2020	6.8	5.4	11.9	8.5	11.7	11.8	7.0
SARS-CoV-2 viral load (copies/mL)	$2.77x10^4$	NA	$2.58x10^3$	$8.28x10^2$	$3.82x10^7$	$1.28x10^4$	$1.36x10^7$
Creatinine (mg/dL)	2.08	0.70	0.79	0.71	2.93	1.01	0.6
Alanine transaminase (U/L)	97.3	15.3	24.6	35.3	46.0	29.2	16
Aspartate aminotransferase (U/L)	958	12	36	32	15	48	13
Creatine Kinase (U/L)	>426,700	NA	279	NA	187	NA	43
Complications	Transaminitis, acute kidney injury	None	Respiratory distress	None	Mixed HHS and DKA, severe COVID-19 pneumonia, heart failure, transaminitis	None	None
Severity of diabetic ketoacidosis	None	None	None	None	Moderate	None	None
Initial venous blood gas pH	7.43	NA	7.47	NA	7.18	NA	NA
Serum bicarbonate (mmol/L)	20	29	24	24	9	19	24
Serum glucose (mg/dL)	106	92	204	92	2238	336	112
Urine ketones	–	–	–	–	–	2+	NA

Abbreviations: T2DM = Type 2 diabetes mellitus; BMI = Body mass index; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; NA = Not available; DKA = Diabetic ketoacidosis; HTN = Hypertension; HHS = Hyperosmolar hyperglycemic state; OSA = Obstructive sleep apnea.

with diabetes and COVID-19 experience serious life-threatening complications. Furthermore, the influence of the ongoing surge driven by the Delta variant of SARS-CoV-2 on diabetes in children, especially in the southern U.S. with a higher proportion of infections in children and adolescents, needs to be examined.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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