



Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes During the COVID-19 Pandemic

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Diabetes Care 2021;44:1451–1453 | <https://doi.org/10.2337/dc20-2733>

OBJECTIVE

The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) on the incidence of new-onset type 2 diabetes and diabetic ketoacidosis (DKA) is unclear. It is unknown whether the coincidence of DKA noted in adult patients with type 2 diabetes is an issue for youth during the coronavirus disease 2019 pandemic.

RESEARCH DESIGN AND METHODS

A retrospective single-center medical record review was conducted in a large, urban children's hospital of pediatric subjects presenting with new-onset type 2 diabetes between March and August of 2018 to 2020.

RESULTS

The proportion of subjects presenting with new-onset type 2 diabetes in DKA dramatically increased in 2020 (9% in 2018, 3% in 2019, and 20% in 2020, $P = 0.029$).

CONCLUSIONS

In 2020, youth with new-onset type 2 diabetes had a greater incidence of DKA at presentation than previously observed. Future studies should examine the impact of SARS-CoV2 exposure on the presentation of type 2 diabetes in all age-groups to inform better patient care.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic challenges our understanding of diabetes across the life span. There appears to be a bidirectional interaction between SARS-CoV2 and diabetes. It is unclear whether SARS-CoV2 directly infects β -cells or whether a combination of immune response dysfunction, inflammation, and increased coagulation activity potentially triggers the development or worsening of diabetes (1–4).

Studies examining the impact of coronavirus disease 2019 (COVID-19) on type 2 diabetes have centered on adults. The impact of COVID-19 on pediatric type 2 diabetes remains unclear. Data from multiple countries suggest that diabetes or new-onset hyperglycemia are poor prognostic indicators for COVID-19 patients (4–7). Reports estimated that 10–55% of adults hospitalized with COVID-19 have diabetes (5). Given the disproportionate increase in the prevalence of obesity and type 2 diabetes in Latinx and African American youth, the potential impact of COVID-19 on

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Received 6 November 2020 and accepted 18 March 2021

This article is part of a special article collection available at <https://care.diabetesjournals.org/collection/diabetes-and-COVID19>.

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minority youth is consequential and disproportionate and places them at significant risk for adverse clinical outcomes (8,9).

For this study, we hypothesized that incidence rates and severity of new-onset type 2 diabetes in youth have increased during the COVID-19 pandemic. We conducted a retrospective medical record review to determine the rate of DKA in patients with new-onset type 2 diabetes in a cohort of ethnically diverse youth from a large, urban children's hospital. Records from March through August of 2018 to 2020 were reviewed.

RESEARCH DESIGN AND METHODS

A single-center retrospective medical record review was conducted for patients newly diagnosed with type 2 diabetes between 1 March and 31 August of 2018, 2019, and 2021 at Children's Hospital Los Angeles (CHLA). The data review and analysis were in compliance with regulations set forth by the CHLA Institutional Review Board (Los Angeles, CA). Type 2 diabetes was diagnosed as previously described (10,11). The diagnosis of DKA was based on pH <7.3 and/or bicarbonate level <15 mmol/L. Ethnicity and race were self-reported and collected from the hospital electronic medical record.

Statistical analysis was performed in Prism 9 software. The χ^2 test for trend (Cochran-Armitage method) was used to calculate statistical significance for categorical variables. One-way ANOVA or the Kruskal-Wallis test was used for normally (age, BMI) or nonnormally (hemoglobin A_{1c} [HbA_{1c}]) distributed continuous variables, respectively. Normality was determined using the D'Agostino and Pearson test. For analysis using continuous variables, mean and SD was used for variables with normal distribution and median and interquartile range (IQR) was used for variables with nonnormal distribution. A 5% level of significance was used for all tests.

RESULTS

Incidence of New-Onset Type 2 Diabetes Increases Over Time

To determine the impact of the COVID-19 pandemic on the incidence of pediatric type 2 diabetes, we determined the number of patients with new-onset type 2 diabetes who presented to CHLA

between 1 March and 31 August in 2018, 2019, and 2020 (Table 1). The ascertainment methods were consistent over the 3 years. Our data captured a steady rise in patients with new-onset type 2 diabetes, from 44 in 2018 to 82 in 2020. Study subjects self-identified primarily as non-White, with between 55% and 82% identifying as Latinx. The mean age at diagnosis, sex distribution, and percentage of patients with a BMI >95th percentile was not significantly different throughout the study periods. The median HbA_{1c} at diagnosis differed across the 3 years ($P = 0.0267$) but was comparable between 2020 and 2018. Pancreatic antibody serology was positive in only 1–5% of all patients, indicating that the observed increase in patients with type 2 diabetes was not due to misinclusion of subjects with type 1 diabetes.

Increased Incidence of DKA in Patients With New-Onset Type 2 Diabetes

We determined the prevalence of DKA among youth with type 2 diabetes across 2018–2020. Our data revealed that the prevalence of DKA increased from <10% in 2018–2019 to 20% in 2020 ($P = 0.0290$). There were no reports of severe DKA cases in 2018 or 2019, but two subjects presented in severe DKA in 2020. All subjects with DKA had negative pancreatic antibody serology.

SARS-CoV2 Status in Patients With New-Onset Diabetes

Patients admitted for DKA were tested for SARS-CoV2 antigen by PCR test. No subject tested positive. Six patients were tested for SARS-CoV2 IgG serology, and two were positive. One patient developed multiple inflammatory syndrome in children (12). The other patient was a 17-year-old boy who presented in DKA but did not report COVID-19 symptoms and was presumed to have had an asymptomatic infection.

CONCLUSIONS

This is the first report on the incidence of new-onset type 2 diabetes in youth since COVID-19 became prevalent in the U.S. We observed an expected and persistent increase in new-onset type 2 diabetes cases that started before the

pandemic, across the same 6-month period for 3 consecutive years. While DKA was a rare occurrence among youth with type 2 diabetes in previous years, we observed a dramatic spike in DKA among new-onset patients during the COVID-19 pandemic. No patients in DKA had active SARS-CoV2 infection. We find it concerning that of the six new-onset patients that were tested, two patients had positive SARS-CoV2 IgG serology. Our findings warrant large-scale registry studies to explore the impact of the COVID-19 pandemic on the development of DKA in new-onset type 2 diabetes in youth.

Our conclusions are constrained by several limitations. The retrospective design restricted our investigation to examining the association between the COVID-19 pandemic and new-onset diabetes but did not allow for inference of causal relationships between these variables. The design also omitted consideration of variable unmeasured or uncontrolled biases (such as family history, referral bias to a specialized clinic, or history of symptoms before presentation) that may influence the observed differences in DKA presence in new-onset type 2 diabetes. The increased incidence of DKA may have resulted in weight loss before presentation, thus underestimating the 2020 subject baseline BMI. Finally, compared with 2018, an increased number of patients did not self-identify their ethnicity and race ("unknown") in 2019 and 2020, precluding us from inferring any relationship between ethnicity and race on the change in DKA incidence.

The incidence of DKA in new-onset type 2 diabetes during the COVID-19 pandemic is significantly higher than historical trends. The exact reason for this increase is unclear. The stringency and duration of "safer-at-home" orders imposed because of the pandemic may have delayed patients and families from seeking medical care until the severity of presentation was dire. It is unknown whether the rise in DKA stems from previous COVID-19 exposure, which disproportionately affects minorities and/or the working poor. Unfortunately, we were unable to infer the relationship between prior SARS-CoV2 exposure and the subsequent diagnosis of type 2 diabetes because SARS-CoV2 serology

Table 1—Characteristics of patients with new-onset diabetes

	2018	2019	2020	P value
Age, years (mean ± SD)	13.5 ± 2.4	14.2 ± 2.5	14.0 ± 2.6	0.3462
HbA _{1c} , % (IQR)	10.3 (5.0)	8.3 (5.4)	10.4 (4.1)	0.0267
HbA _{1c} , mmol/mol (IQR)	89 (31)	67 (36)	90 (21)	
%BMI _{p95}	128 ± 31	129 ± 28	135 ± 31	0.2765
Ethnicity, n (%)				0.0065
Latinx	36 (82)	44 (67)	45 (55)	
Non-Latinx	7 (16)	7 (11)	13 (16)	
Unknown	1 (2)	15 (22)	24 (29)	
Race, n (%)				NA
White	7 (16)	16 (24)	15 (18)	
Black	3 (7)	3 (5)	7 (9)	
Asian	2 (5)	2 (3)	2 (2)	
Native American/Eskimo	0 (0)	0 (0)	1 (1)	
Other	31 (70)	35 (53)	47 (57)	
Unknown	1 (2)	10 (15)	10 (12)	
New-onset patients, n (% female)	44† (57)	66 (55)	82 (46)	NA
DKA, n (%)	4 (9)	2 (3)	16 (20)	0.0290
Severe DKA (DKA/new), n (%)	0/44 (0)	0/66 (0)	2/82 (2)	NA
Pancreatic antibody, n (%)				NA
Positive	2 (5)	2(3)	1 (1)	
Negative	35 (80)	61(92)	74 (90)	
Not done	7 (16)	3(5)	7 (9)	
SARS-CoV2 prevalence in DKA‡				NA
SARS-CoV2 PCR ⁺ , n (%)	—	—	0/14 (0)	
SARS-CoV2 IgG, n (%)	—	—	2/6 (33)	

Bold P values are statistically significant ($P < 0.05$). %BMI_{p95}, excess percent of the 95th percentile. NA, not applicable. †No information was available on whether one patient was in DKA at diagnosis. ‡Only subjects admitted as inpatients to CHLA for DKA were tested.

testing was not a clinically warranted measurement in the course of normal new-onset diabetes care. In the limited number of SARS-CoV2 serology tests performed in the subjects, one-third were positive for previous COVID-19 exposure. It remains unknown whether prior COVID-19 exposure contributes to increased diabetes severity and reinforces the need for further investigation.

The strengths of the current study include the use of data from a large, urban, diverse pediatric population and comparison with historical data collected during the same time period over the previous 2 years. Because this was only a single-center experience, it is unclear whether the observed relationships extend to age-matched cohorts elsewhere. Our conclusions warrant replicating and extending this study,

because the impact of COVID-19 exposure on β -cell function and the development of diabetes in pediatric patients remains understudied.

Acknowledgments. The authors are grateful to the clinical faculty in the Division of Endocrinology and Metabolism (CHLA, Los Angeles, CA) for their insightful observations that contributed to the conception of this manuscript.

Funding. A.P.V. receives funding from the National Institutes of Health/National Center for Research Resources, Southern California Clinical and Translational Science Institute grant number UL1 TR000130, and S.G. from American Diabetes Association 7-20-COVID-173 and the Homer and Gloria Harvey Family Foundation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. L.C.C., A.P.V., and S.G. conceptualized and designed the study,

drafted the initial manuscript, and reviewed and revised the manuscript. L.C.C. performed the statistical analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. L.C.C. and S.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Drucker DJ. Coronavirus infections and type 2 diabetes—shared pathways with therapeutic implications. *Endocr Rev* 2020;41:457–470
- Rabizadeh S, Hajmiri M, Rajab A, Emadi Kouchak H, Nakhjavani M. Severe diabetic ketoacidosis and coronavirus disease 2019 (COVID-19) infection in a teenage patient with newly diagnosed diabetes. *J Pediatr Endocrinol Metab* 2020;33:1241–1243
- Reddy PK, Kuchay MS, Mehta Y, Mishra SK. Diabetic ketoacidosis precipitated by COVID-19: a report of two cases and review of literature. *Diabetes Metab Syndr* 2020;14:1459–1462
- Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in Covid-19. *N Engl J Med* 2020; 383:789–790
- Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab* 2020;31:1068–1077.e3
- Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes: lessons learned for our future (an experience to be used). *Diabetes Res Clin Pract* 2020;162: 108137
- Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020;109: 531–538
- Alcendor DJ. Racial disparities-associated COVID-19 mortality among minority populations in the US. *J Clin Med* 2020;9:2442
- Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among Black patients and White patients with Covid-19. *N Engl J Med* 2020;382:2534–2543
- American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2019*. *Diabetes Care* 2019;42(Suppl. 1):S13–S28
- Chang N, Yeh MY, Raymond JK, Geffner ME, Ryoo JH, Chao LC. Glycemic control in youth-onset type 2 diabetes correlates with weight loss. *Pediatr Diabetes* 2020;21: 1116–1125
- Naguib MN, Raymond JK, Vidmar AP. New onset diabetes with diabetic ketoacidosis in a child with multisystem inflammatory syndrome due to COVID-19. *J Pediatr Endocrinol Metab* 2020;34:147–150