



Comparison of Diabetic Ketoacidosis in Adults During the SARS-CoV-2 Outbreak and Over the Same Time Period for the Preceding 3 Years

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Diabetic ketoacidosis (DKA) is a life-threatening metabolic decompensation occurring with any diabetes subtype, often precipitated by infection. During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, reports emerged suggesting that coronavirus disease 2019 (COVID-19) is associated with a higher frequency of DKA with atypical presentations (1,2) and led some to hypothesize a direct effect of SARS-CoV-2 on the pancreas itself (3).

We addressed the observational bias of such reports by comparing DKA cases and characteristics in adults during the outbreak to matched 4-month periods (1 February–31 May) from 2017 to 2019 at a large London National Health Service (NHS) Trust.

Analyzing 175 biochemically confirmed DKA cases, the 3-year average for patients admitted over the 4-month period was 44 (exact Poisson CI 32–59) vs. 43 (31–58) during the outbreak. Although adult medical admissions reduced by 33% (3-year average for the same time period 26,831 vs. 19,267), the proportion of individuals presenting with DKA during the outbreak was 0.22% of all admissions compared with a 3-year average of 0.16% ($P = 0.16$).

Among those presenting with DKA, the proportion with a diagnosis of type 2

diabetes during the SARS-CoV-2 outbreak was higher compared with the preceding 3 years (37% vs. 17%, $P = 0.01$) (Table 1), and proportion with type 1 diabetes reduced from 68% pre-pandemic to 44%. Adults with type 2 diabetes had a significantly higher proportion of positivity for SARS-CoV-2 than those with other types of diabetes—89% vs. 27%, respectively ($P = 0.009$).

Adults ($n = 43$) presenting during the outbreak were older than those ($n = 132$) in preceding years (median age 53 vs. 44 years, $P = 0.03$) and fewer were insulin treated (89% vs. 60%, $P < 0.0001$).

Comparing $n = 89$ adults in DKA with type 1 diabetes prepandemic to $n = 19$ during the outbreak, we observed no significant differences in demographic characteristics or biochemical characteristics of DKA (pH, ketone, or bicarbonate level) and noted markedly elevated HbA_{1c} (11.1% [98 mmol/mol] prepandemic vs. 12.9% [118 mmol/mol], $P = 0.1$) across both time frames.

Adults ($n = 22$) with type 2 diabetes in DKA during the outbreak were of similar age to those prepandemic (69 vs. 63 years, $P = 0.5$), and no demographic or biochemical differences were observed including use of sodium–glucose cotransporter 2 inhibitors (Table 1).

People with type 2 diabetes in DKA who had COVID-19 ($n = 8$) were more likely to be of non-White ethnicity (100% vs. 35%, $P = 0.015$) than patients prepandemic ($n = 22$) and equally likely to not be insulin treated (50% vs. 50%). In total, 5 of 43 (12%) individuals (all with type 2 diabetes and 4 of 5 with COVID-19) died during their admission with DKA compared with 3 of 130 (2.3%) prepandemic ($P = 0.023$) (Table 1). Those who died had significant comorbidities or multiorgan failure at admission and were not deemed appropriate for intensive care or ventilatory support.

In this systematic analysis of DKA presentations during the COVID-19 pandemic compared with previous years, no significant changes in absolute numbers of DKA cases were observed, but adults with type 2 diabetes disproportionately contributed to cases. The presentations of DKA in people with type 2 diabetes were significantly associated with SARS-CoV-2 infection, while the proportion of people presenting in DKA with known type 1 diabetes reduced and they were less likely to test positive.

We hypothesize that the characteristics of those overrepresented in the DKA cohort during the pandemic reflect the characteristics of those most at risk for the severe manifestations of

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Table 1—Proportion of patients presenting with DKA during the COVID-19 outbreak and in comparison with the 4-month period from 1 February to 31 May between 2017 and 2019. Subanalysis by subtype of diabetes and SARS-CoV-2 status along with treatment and mortality data. *P* values derived using a Fisher exact test.

	Total, 2017– 2019	During outbreak	<i>P</i> (before vs. during outbreak)	Tested for SARS-CoV-2	SARS-CoV- 2–positive	SARS-CoV-2– negative	<i>P</i> (positive vs. negative)
Total DKA cases (biochemically confirmed)	133	43		24 (56)	12 (50)	12 (50)	
Subtypes of diabetes							
Known type 1 diabetes	89 (68)	19 (44)	0.019**	9 (47)	1 (11)	8 (89)	0.002**
Known type 2 diabetes	22 (17)	16 (37)		9 (56)	8 (89)	1 (11)	
Known other type	4 (3)	2 (5)		2 (100)	1 (50)	1 (50)	
New presentation	15 (12)	6 (14)#		4 (67)	2 (50)	2 (50)	
All non–type 2 diabetes	108 (83)	27 (63)	0.01*	15 (56)	4 (27)	11 (73)	0.009*
All known diabetes	115 (88)	37(86)	0.79\$	20 (54)	10 (50)	10 (5)	1.0\$
Treatment of type 2 diabetes at admission							
Insulin treated	11 (58)	6 (38)	0.32	—	—	—	—
SGLT2 inhibitor	3 (14)	1 (6)	0.62	—	—	—	—
Mortality							
Overall	3/130 (2.3)	5/43 (12)	0.023	4/5 (80)	4/4 (100)	0	—
Type 2 diabetes	2/22 (9)	5/16 (31)	0.12	4/5 (80)	4/4 (100)	0	—

Data are *n* or *n* (%). SGLT2, sodium–glucose cotransporter 2. ***P* value for comparison of the distribution of different subtypes of diabetes. *Statistical comparison of all non–type 2 diabetes vs. type 2 diabetes. \$Statistical comparison of DKA cases in all individuals with known diabetes versus DKA cases in those with new diabetes presentation. #Of the six newly diagnosed individuals, reviewed retrospectively, three had type 1 diabetes (positive pancreatic autoantibodies), one had type 2 diabetes, one had pancreatic type 3c diabetes, and the final developed insulin-deficient diabetes after immune checkpoint inhibitor use, with negative autoantibodies. The checkpoint inhibitor patient and one patient with type 1 diabetes were positive to SARS-CoV-2.

COVID-19 (4): older individuals with sub-optimal glycemic control and a propensity toward people from non-White ethnic groups among those with COVID-19. A study of *n* = 35 hyperglycemic emergencies (2) in SARS-CoV-2–positive patients supports our observation of excess type 2 diabetes presentations.

The “stress response” associated with COVID-19 may account for the higher proportion of DKA in those with type 2 diabetes; relative insulin deficiency from rising glucagon and cortisol contributes to DKA development, particularly in those not insulin treated. Excess DKA was noted in a previous influenza epidemic when ~70% of the typical DKA cases/year occurred in an 8-week period (5), suggesting DKA in at-risk individuals may be an expected feature of any severe viral infection.

We observed no differences in the biochemical characteristics or severity of DKA; however, despite this, a higher death rate was observed, specifically in those with COVID-19. With larger numbers, biochemical differences may emerge, but the higher frequency of type 2 diabetes may account for observations of “atypical presentations” as practitioners may be more accustomed

to managing DKA in people with type 1 diabetes.

We acknowledge national testing strategies employed early in the outbreak may have missed some cases of COVID-19. Until 26 April, specific criteria had to be met (fever, cough, breathlessness) to be tested, but beyond that date all admissions were tested.

In conclusion, the SARS-CoV-2 outbreak was associated with similar numbers of DKA cases in adults compared with previous years. However, a higher proportion of cases occurred in older individuals with type 2 diabetes who were less likely to be insulin treated, and these presentations were specifically associated with positivity for SARS-CoV-2 in non-White ethnic groups. Further work is needed to determine whether this finding represents a specific SARS-CoV-2 effect on the β -cell or if these cases reflect the effects of widespread infection on risk of DKA in susceptible individuals.

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