Received: 3 July 2020 | Accepted: 1 October 2020

DOI: 10.1111/dme.14416

DIABETIC Medicine

LETTER

Diabetic emergencies during the COVID-19 pandemic: A case–control study

Initial reports have suggested that COVID-19 SARS 2 virus is more prevalent and is associated with increased severity in people with diabetes.[1] In a recent large series from the USA, diabetes mellitus was present as a comorbidity in over a third of patients hospitalized with COVID-19.[2] In a study of 658 hospitalized patients with confirmed COVID-19, three developed diabetic ketoacidosis (DKA).[3] Clinical experience during the COVID-19 crisis suggests that DKA and hyperglycaemic hyperosmolar syndrome (HHS) are common in people with COVID-19 infection, and are associated with significant insulin resistance, dehydration and acute kidney injury.

We performed a case–control study of COVID-19-positive diabetes emergencies presenting to a single centre, compared with a group of non-COVID-19 controls. DKA was defined as glucose >11 mmol/l, pH ≤7.3, capillary ketones ≥3.0 mmol/l or urine ketones ≥2+. HHS was a clinical diagnosis with significant hyperglycaemia and calculated osmolality [2 × (Na + K) + urea ≥320 mOsmol/kg]. Cases were positive for COVID-19 on nasal/throat swabs. Each case was compared with two non-COVID-19 cases of DKA and HHS prior to the coronavirus outbreak. We also compared the estimated frequency of cases presenting per month.

Continuous variables were compared using Student's *t*-test or the Mann–Whitney test. Categorical variables were compared using a chi-squared test or Fisher's exact test. Two-sided P values <0.05 were taken to indicate statistical significance. Formal analyses were not performed where the frequency of a categorical variable was very low (≤1), but frequencies are shown.

A total of 21 diabetes emergencies presented between March and April 2020, of which four were COVID-19-negative (DKA, $n = 3$; HHS, $n = 1$). The characteristics, clinical progress and outcomes of the 17 (DKA, $n = 7$; HHS, $n = 10$) COVID-19-positive patients are shown in Table 1. COVID-19 cases with DKA were similar in gender, but significantly older than non-COVID controls (52.1 ± 13.4 vs 32.4 ± 11.6 years; $P = 0.01$) and were of black or south-east Asian ethnicity. There were more cases with type 2 diabetes (71% vs 8%; $P = 0.005$), but only two with SGLT2 inhibitor use (postulated as a risk factor). The COVID-19 cases had more comorbidities than controls, a longer length of stay [10 (5–22) vs 1 (1–3) days; $P = 0.004$] and more frequently needed critical care (72% vs 7%; $P = 0.006$). The cases also had higher glucose [35 (31–43) vs 25.4 (20.3–31) mmol/l; $P = 0.01$] and higher peak sodium levels (148 ± 15 vs 138 ± 3 mmol/l; $P = 0.03$). Complications included pulmonary embolus, acute kidney injury and one patient died. Monthly admission frequency was 10/month for cases and 9.6/month for controls. We did not identify any episodes of euglycaemic DKA. Our electronic patient record search for control data could potentially have missed euglycaemic DKA if this had not been correctly coded as DKA on the discharge summary. However, during the COVID-19 pandemic peak period, there were consultant-led diabetes ward rounds daily, and consultant presence for 12 h/day; we are confident that we would have been aware of any cases of potential euglycaemic DKA presenting to our hospital over that time period.

There were five cases of DKA with type 2 diabetes. Two of these individuals were of black and three were of Asian ethnicity, their mean age was 60.4 ± 3.1 years, their mean duration of diabetes was 19.2 ± 5.4 years (one was a new diagnosis) and their median (interquartile range) HbA_{1c} concentration was 95 (81-110) mmol/mol [10.8 (9.6-12.2)%]. Two patients were on oral medication (double/quadruple therapy) with poor glycaemic control and two were taking insulin (twice- daily/basal-bolus). Three had macrovascular complications (ischaemic heart disease, cerebrovascular disease) and three had microvascular complications (retinopathy, neuropathy).

Individuals with HHS and COVID-19 had comparable gender, age and type of diabetes to the control non-COVID patients. Biochemical markers at presentation were similar in the two groups, as was overall management. There were more complications in controls, but mortality was the same, at 20%. The admission rate for HHS was 11/month for cases compared with 1.4/month for controls, representing a seven-fold higher rate.

A brief case series of hyperglycaemic crises has also been reported,[4] but the present study is the first case–control study in this population. COVID-19 infection is associated with an atypical presentation of DKA with higher glucose and high sodium in older patients with comorbidities and type 2 diabetes. HHS presents more typically, but is markedly increased in frequency. Clinicians should check ketones in all patients

TABLE 1 Characteristics, presenting features, management and outcomes of cases and controls.

	COVID−19-positive group	Control group	*P*
DKA	*N* = 7	*N* = 14	
Gender: male, *n* (%)	6 (85)	8 (57)	0.2
Age, years	52.1 ± 13.4*	32.4 ± 11.6*	**0.01**
Ethnicity, *n* %			n/a‡
White	0	11 (78)	
Black	4 (57)	0	
Asian	3 (42)	3 (22)	
New-onset diabetes, *n* (%)	2 (28)	0	n/a
Type of diabetes, *n* (%)			**0.005**
Type 1	2 (28)	13 (92)	
Type 2	5 (71)	1 (8)	
HbA_{1c}			0.77
mmol/mol	79 (65–104)	84 (73–107)	
%	9.4 (8.1–11.7)	9.8 (8.8–11.9)	
Prior comorbidities, *n* (%)		None	n/a
Macrovascular§	3 (30)		n/a
Microvascular¶	2 (30)		
SGLT2 inhibitor use, *n* (%)	2 (28)	0	n/a
Highest glucose value, mmol/l	35 (31–43)†	25.4 (20.3–31)†	**0.01**
Lowest pH	7.18 (6.94–7.23)†	7.25 (7.14–7.27)†	0.1
Highest sodium, mmol/l	148 ± 15	138 ± 3	**0.03**
Mixed DKA/HHS**, *n* (%)	1 (14)	0	n/a
Critical care admission	5 (72)	1 (7)	**0.006**
Complications, *n* (%)			0.3
Pulmonary embolism	1 (14)	0	
Acute kidney injury	2 (28)		
Length of stay, days	10 (5–22)†	1 (1–3)†	**0.004**
Mortality, *n* (%)	1 (14)	0	n/a
HHS	*N* = 10	*N* = 20	
Gender: male, *n* (%)	7 (70)	15 (75)	0.8
Age, years	67.6 ± 10.5*	67 (56–79)†	0.7
Ethnicity, *n* (%)			n/a
White	3 (30)	8 (40)	
Black	6 (60)	6 (30)	
Asian	1 (10)	6 (30)	
New-onset diabetes, *n* (%)	1 (10)	3 (15)	n/a
Type of diabetes, %			1
Type 1	0	0	
Type 2	100	100	
HbA_{1c}			0.6
mmol/mol	79 (66–85)	84 (73–107)	
%	9.4 (8.2–9.9)	9.8 (8.8–11.9)	
Prior comorbidities, *n* (%)			
Respiratory	2 (20)	5 (25)	0.8

(Continues)

TABLE 1 (Continued)

	COVID−19-positive group	Control group	*P*
Macrovascular[§]	3 (30)	11 (55)	0.2
Microvascular[¶]	1(10)	4 (20)	0.6
Neurological	0	2 (10)	0.1
Hypertension	8 (80)	9 (45)	0.08
SGLT2 inhibitor use, *n*	0	0	
Highest glucose value, mmol/l	39.9 ± 15.5*	50 (36–56)[†]	0.1
Lowest pH	7.34 ± 0.08*	7.27 (7.17–7.39)[†]	0.08
Highest sodium value, mmol/l	159 (155–164)[†]	154 ± 14*	0.3
Mixed DKA/HHS[††], *n* (%)	4 (40)	5 (25)	0.43
Critical care admission	4 (40)	15 (75)	0.08
Complications, *n* (%)			0.3
Acute kidney injury	2 (20)	8 (40)	0.5
Cerebrovascular accident	1 (10)	4 (20)	
Length of stay, days	12 (10–18)[†]	12 (6–17)[†]	0.72
Mortality, *n* (%)	2 (20)	4 (20)	1

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperglycaemic hyperosmolar syndrome, n/a, not applicable; SGLT2, sodium-glucose co-transporter-2.
[*]Mean ± SD, where data are normally distributed.[†]Median (interquartile range).[‡]Analyses not performed due to low frequencies.[§]Ischaemic heart disease, cerebrovascular disease, peripheral vascular disease.[¶]Retinopathy, neuropathy, nephropathy. **Glucose ≥50 mmol/l.[††]Capillary ketones ≥3.0 mmol/l. Univariate unadjusted analyses are shown.

with suspected COVID-19 infection, hyperglycaemia and acidosis, and be alert to the increased frequency of HHS.

COMPETING INTERESTS

None declared.

FUNDING INFORMATION

None.

M. S. B. Huda[1]
S. Shaho[1]
B. Trivedi[1]
G. Fraterrigo[1]
L. Chandrarajan[1]
P. Zolfaghari[2]
T. M. Dovey[3]
C. G. Garrett[1]
T. A Chowdhury[1]

[1]*Department of Diabetes and Metabolism, St Bartholomew's and Royal London Hospitals, London, UK*
[2]*Adult Critical Care Unit, Royal London Hospital, Barts Health NHS Trust, London, UK*
[3]*Department of Psychology, Brunel University of London, London, UK*

Correspondence
M. S. B. Huda, Department of Diabetes and Metabolism, St Bartholomew's and Royal London Hospitals, London, UK.
Email: bobby.huda1@nhs.net

ORCID

M. S. B. Huda https://orcid.org/0000-0001-7303-199X
C. G. Garrett https://orcid.org/0000-0003-4425-6609
T. A Chowdhury https://orcid.org/0000-0001-8878-2331

REFERENCES

1. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr*. 2020;14:303-310.
2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323:2052-2059.
3. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab*. 2020; https://doi.org/10.1111/dom.14057. Online ahead of print.
4. Kim NY, Ha E, Moon JS, Lee YH, Choi EY. Acute Hyperglycemic Crises with Coronavirus Disease-19: Case Reports. *Diabetes Metab J*. 2020;44:349-353.