Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series

Diabetes is a major contributor to disease severity and mortality in patients with COVID-19; with an estimated 3·5-times increase in risk of death during hospital admission for patients with type 1 diabetes, and 2·03-times for those with type 2 diabetes.[1] Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are hyperglycaemic emergencies associated with substantial mortality.[2] Observations retrieved from the Chinese population describe ketosis or ketoacidosis to be common among patients admitted with diagnosis of COVID-19, and potentially modifying the clinical outcome.[3] However, to date there is paucity of data on the characteristics of hyperglycaemic emergencies occurring in the context of COVID-19.

According to our knowledge, we report the first case series of hyperglycaemic emergencies hospitalised during the COVID-19 outbreak in the UK.

This retrospective analysis recruited eligible patients from three hospitals in north London, UK, March 1–30, 2020 (appendix, p 1). 35 patients with COVID-19, presenting with DKA (31·4%), mixed DKA and HHS (37·1%), HHS (5·7%), or hyperglycaemic ketosis (25·7%) were included and evaluated (table). The median age of the patients was 60 years (IQR 45–70) and the median BMI was 23·5kg/m² (IQR 20·7–27·3). Type 2 diabetes was prevalent in 28 (80%), whereas 2 (5·7%) of 35 patients were new presentation of diabetes. Previous history of DKA was found in 5 patients with type 1 disease. Median overall HbA_{1c} was 111 mmol/mol (IFCC; diabetes diagnostic cut-off ≥48 mmol/mol). With regards to ethnicity, 40% of patients were African, 20% Caucasian, 17·1% of mixed ethnic origin, and 14·3% Asian (5·7% of Chinese and 8·6% of Indian origin).

Before hospital admission 12 (34·3%) of 35 of patients were on insulin treatment. Two patients (5·7%) were on SGLT2 inhibitor treatment and presented with mixed DKA and HHS. A total of 12 patients (34·3%) were treated with slower fluid administration compared to the algorithm in the National DKA and HHS guidance, due to underlying diagnosis of acute respiratory distress syndrome. Myocarditis was identified

Lancet Diabetes Endocrinol 2020
Published Online
July 1, 2020
https://doi.org/10.1016/S2213-8587(20)30221-7

See Online for appendix

	All cases (n=35)	DKA (n=11)	Mixed DKA and HHS (n=13)	Hyperglycaemic ketosis (n=9)	HHS (n=2)
Demographic and anthropometric parameters					
Sex					
Male	77·1% (27)	63·6% (7)	23·1% (3)	44·4% (4)	0% (0)
Female	22·9% (8)	36·4% (4)	76·9% (10)	55·6% (5)	0% (0)
Age (years)	60 (45 to 70)	57 (48 to 64)	54 (42 to 85)	63 (36 to 77)	69 (65 to 72)
BMI (kg/m²)	23·5 (20·7 to 27·3)	24·7 (21·3 to 28·5)	22·7 (22·2 to 27·9)	26·0 (23·6 to 27·4)	25·4 (21·9 to 27·6)
Ethnicity					
African	40·0% (14)	45·4% (5)	30·7% (4)	33·3% (3)	100% (2)
Afro-Caribbean	8·6% (3)	0% (0)	15·4% (2)	11·1% (1)	0% (0)
Asian—Chinese	5·7% (2)	9·1% (1)	7·7% (1)	0% (0)	0% (0)
Asian—Indian	8·6% (3)	0% (0)	7·7% (1)	22·2% (2)	0% (0)
Caucasian	20·0% (7)	27·3% (3)	23·1% (3)	11·1% (1)	0% (0)
Mixed	17·1% (6)	18·2% (2)	15·4% (2)	22·2% (2)	0% (0)
Medical background					
Type of diabetes					
Type 1	14·3% (5)	18·2% (2)	15·4% (2)	11·1% (1)	0% (0)
Type 2	80·0% (28)	81·8% (9)	76·9% (10)	88·9% (8)	50·0% (1)
New presentation	5·7% (2)	0% (0)	7·6% (1)	0% (0)	50·0% (1)
ARB or ACE inhibitor	40·0% (14)	27·3% (3)	53·8% (7)	44·4% (4)	0% (0)
Metformin	65·7% (23)	90·9% (10)	61·5% (8)	33·3% (3)	100% (2)
DPP-4 inhibitor	25·7% (9)	36·3% (4)	15·4% (2)	33·3% (3)	0% (0)
SGLT2	5·7% (2)	0% (0)	15·4% (2)	0% (0)	0% (0)
Insulin	34·3% (12)	18·2% (2)	61·5% (8)	11·1% (1)	50·0% (1)

(Table continues on next page)

	All cases (n=35)	DKA (n=11)	Mixed DKA and HHS (n=13)	Hyperglycaemic ketosis (n=9)	HHS (n=2)
(Continued from previous page)					
Biochemical parameters at admission					
Serum β-hydroxybutyrate (mmol/L)	5·0 (3·0 to 6·4)	6·0 (4·0 to 6·1)	6·5 (5·0 to 7·2)	2·1 (1·2 to 3·0)	6·0 (5·0 to 7·0)
Time to ketone resolution (h)	24 (15 to 36)	35 (24 to 60)	29 (22 to 48)	10 (6 to 24)	36 (35 to 36)
Osmolality (mosm/kg)	304 (292 to 333)	301 (294 to 303)	334 (326 to 359)	299 (292 to 304)	336 (324 to 347)
Urea (mmol/L)	10·1 (6·1 to 20·5)	7·7 (4·2 to 8·6)	17·1 (7·1 to 23·1)	6·1 (3·7 to 14·3)	9·7 (9·2 to 0·1)
Creatinine (mmol/L)	138 (95 to 232)	110 (80 to 127)	170 (113 to 277)	113 (63 to 201)	82 (67 to 96)
EGFR	47 (23 to 71)	66 (48 to 76)	42 (21 to 65)	38 (25 to 67)	81 (71 to 90)
Glucose (mmol/L)	28 (18 to 35)	27 (22 to 31)	35 (28 to 39)	18 (14 to 30)	35 (33 to 37)
HbA_{1c}					
mmol/mol	111 (90 to 132)	112 (93 to 132)	112 (88 to 147)	93 (79 to 118)	88 (83 to 92)
%	12·3 (10·4 to 14·2)	12·4 (10·7 to 14·2)	12·4 (10·2 to 15·6)	10·7 (9·4 to 12·9)	10·2 (9·7 to 10·6)
pH	7·3 (7·2 to 7·4)	7·2 (6·9 to 7·3)	7·3 (7·1 to 7·3)	7·4 (7·3 to 7·4)	7·4 (7·4 to 7·5)
Base excess (mmol/L)	−10·1 (−19·0 to −3·2)	−12·6 (−24·9 to −10·4)	−10·2 (−21·1 to −8·8)	−1·4 (−3·0 to 1·97)	−4·05 (−7·8 to −0·3)
Serum bicarbonate (mmol/L)	15·5 (9·2 to 21·2)	11·8 (7·8 to 15·4)	15·5 (7·1 to 17·1)	22·9 (20·1 to 27·0)	19·8 (14·9 to 24·8)
Lactate (mmol/L)	2·5 (1·5 to 3·2)	2·6 (1·5 to 2·9)	3·1 (1·9 to 4·9)	1·7 (1·0 to 2·7)	2·5 (2·3 to 2·6)
Sodium (mEq/dL)	138 (133 to 145)	134 (131 to 136)	141·5 (138 to 158)	139 (136 to 144)	139 (128 to 149)
Potassium (mEq/dL)	5·1 (4·5 to 5·6)	5·4 (4·6 to 6·5)	5·2 (4·5 to 5·9)	4·8 (4·3 to 5·1)	4·45 (3·8 to 5·1)
Anion gap (mEq/L)	12·7 (10·0 to 19·8)	14·8 (10·4 to 20·5)	18 (11·9 to 27·5)	11·1 (7·9 to 15·2)	12·1 (12·0 to 2·5)
Clinical management					
Fluid replacement during 1–4 h (L)	1·8 (1·0 to 2·3)	1·3 (1·1 to 2·0)	1·9 (1·5 to 2·3)	2·2 (1·7 to 2·5)	1·5 (1·0 to 2·0)
Fluid replacement on day 1 (L)	3·5 (3·0 to 4·9)	3·8 (3·0 to 5·0)	5·0 (4·0 to 6·0)	2·0 (1·0 to 2·5)	5·0 (4·0 to 5·8)
Fluid replacement on day 2 (L)	4·0 (2·5 to 5·2)	4·1 (3·0 to 5·3)	2·0 (1·5 to 3·0)	2·5 (1·5 to 3·0)	2·0 (1·5 to 2·8)
Insulin dose day 1 (units/kg per h)	0·07 (0·04 to 0·09)	0·09 (0·06 to 0·15)	0·07 (0·04 to 0·12)	0·05 (0·03 to 0·07)	0·06 (0·02 to 0·11)
Hypoglycaemia during treatment	5·7% (2)	0% (0)	15·4% (2)	0% (0)	0% (0)
Hypokalaemia during treatment	22·8% (8)	36·3% (4)	15·4% (2)	22·2% (2)	100% (2)
Outcome					
Length of stay	12 (4 to 16)	13 (2 to 21)	10 (3 to 38)	13 (3 to 16)	16 (15 to 17)
Intensive care admission	22·8% (8)	27·3% (3)	23·1% (3)	11·1% (1)	50·0% (1)
Mortality	5·7% (2)	9·1% (1)	7·7% (1)	0% (0)	0% (0)

Data are n (%), median (IQR) for all columns except from HHS (n=2) where values are expressed as median (range). DKA=diabetic ketoacidosis. HHS=hyperosmolar hyperglycaemic state. ARB=angiotensin receptor blocker. ACE=angiotensin-converting enzyme. DPP-4=dipeptidyl peptidase-4. SGLT2=sodium-glucose co-transporter-2. EGFR=epidermal growth factor receptor.

Table: **Clinical and biochemical characteristics**

in two patients (5·7%). Median time to ketone resolution for patients with DKA was 35 h (IQR 24–60) (appendix, p 3). Across all cases, the degree of ketonaemia negatively correlated with bicarbonate (strong) and base excess (moderate) (appendix p 2); whereas positively associated with alanine aminotransferase (moderate). Capillary ketone levels and time to resolution according to ethnicity are presented in the appendix (p 3). Time to ketone-resolution was positively associated with prothrombin time, activated partial thromboplastin time, and fluid volume required (strong); whereas, negatively correlated with pH, bicarbonate levels and base excess (moderate, appendix p 2). As per Kaplan-Meier analysis, median time to intensive care unit admission was 3·0 days (95% CI 0·6–5·4), and median length of stay for discharged patients was 18·0 days (95% CI 10·2–25·8; appendix pp 4–5). Severe insulinopenia persisted until discharge for 7 (20%) of 35 patients, previously non-insulin treated. At the time of this report, 13 were still inpatients, whereas 2 [5·7%] of 35 patients, previously non-insulin treated, had died (DKA n=1; mixed DKA and HHS n=1).

This study shows striking type 2 disease overrepresentation in those presenting with DKA, suggesting

acute insulinopenia in patients with COVID-19 and with type 2 diabetes, which persisted up until the time of discharge in 30% of patients previously not insulin-treated. Moreover, our study sample, with almost half of patients of African background, had protracted ketonaemia and ketoacidosis.

Data from China indicate prevalent ketosis in patients admitted with COVID-19, especially among those with diabetes,[3] however, no information is provided regarding the type or treatment of diabetes, or both. Adjusting for COVID-19 severity, Zhu and colleagues, reported HR of 1·4 for all-cause mortality, comparing patients with type 2 diabetes with non-diabetics (95% CI 1·1–1·9), whereas well controlled glycaemia associated with better clinical outcome.[4] The CORONADO study[5] described that BMI is associated with an adverse outcome after COVID-19 infection, at 7 days of admission, independently of glycaemic control.[5] Kim and colleagues, reported a fatal DKA and a delayed recovery HHS case, in Korean patients with COVID-19 infection and known type 2 diabetes.[6]

Our patients developed protracted ketonaemia and ketoacidosis, with median time to ketone resolution in DKA of approximately 35 h; whereas in non-COVID-19 DKA cases the median duration of ketoacidosis is approximately 12 h.[7] Similarly, a case report of DKA in a patient with COVID-19 infection and previously undiagnosed diabetes, describes that ketonaemia resolved after 24 h.[8] According to relative experience from China, presence of ketosis and ketoacidosis in patients with COVID-19 infection was associated with length of hospital admission and overall mortality.[3] Emerging reports suggest substantial insulin resistance and possibly relative insulinopenia in severe COVID-19 disproportionate to that seen in critical illness caused by other conditions,[9] which might have contributed to the metabolic decompensation. In line with these observations, 35% of patients in our study required an increase of the fixed dose insulin infusion above the recommended insulin dose for DKA of 0·1 units/kg per h.[2] The slower fluid administration in the context of co-existing respiratory complications might also explain at least in part the protracted ketonaemia.[2]

According to our findings, an interplay between ethnicity and ketogenesis cannot be excluded. Even though our sample size was small to identify statistical differences, almost half of our sample consisted of patients with African or Afro-Caribbean descent,[10] which might explain at least in part the profound ketonaemia on admission. Our study differs from previous reports, which were limited to single ethnicity.[3,4,6,8]

Limitations of our study include the small sample size, the cross-sectional design, and the retrospective nature of the analysis. Levels of cortisol and c-peptide were not assessed. The collection of information through review of hand-written medical records might have led to reporting and collection bias.

In summary we report that COVID-19 is associated with hyperglycaemic emergencies in COVID-19 with overrepresentation of type 2 diabetes in patients presenting with DKA and long-lasting ketosis. Further large-scale observational studies are needed to elucidate the diabetogenic effects of COVID-19, and the impact of factors such as medication adherence, glycaemic control pre- and during hospitalization and ethnicity on the development of COVID-19.

Finally, future prospective studies are needed to investigate measures to improve adherence to sickness rules, ketone monitoring and management of DKA-risk, which becomes even more relevant ahead of a predicted second SARS-CoV-2 wave of infection.

We declare no competing interests.

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