Title: **Diabetic emergencies during the Covid-19 pandemic – a case control study**

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Word count: 496 (main text) and 95 (abstract)

Conflicts of interest: None declared

Acknowledgements: All authors were employees of Barts Health NHS trust at the time of submitting the manuscript.

Abstract

We describe a single centre experience of diabetes emergencies during the Covid-19 pandemic and these are compared with controls prior to the pandemic. Demographics, clinical progress and outcomes were compared with controls. For diabetic ketoacidosis (DKA) there was a significant increase in patients with type 2 diabetes of ethnic minority origin, with higher glucose, higher sodium and they were more likely to need critical care admission. The monthly frequency was the same as prior to the pandemic. For hyperglycaemic hyperosmolar syndrome (HHS) the patients were similar to controls but the monthly frequency had increased by seven fold.

Key words: Diabetes emergencies, Covid-19, diabetic ketoacidosis, hyperglycaemic hyperosmolar syndrome

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 US, diabetes mellitus was present as a co-morbidity in over a third of patients hospitalised with Covid-19.[2] In a study of 658 hospitalised patients with confirmed Covid-19, three developed diabetic ketoacidosis[3] Clinical experience during the Covid crisis suggests that diabetic ketoacidosis (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 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 x (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 with Student's t-test or Mann-Whitney test. Categorical variables were compared with Chi-squared test or Fisher's exact test. Two-sided p value <0.05 was deemed significant.

Twenty-one diabetes emergencies presented between March-April 2020, of whom four were Covid-19 negative (3 DKA, 1 HHS). The characteristics, clinical progress and outcomes of the 17 (7 DKA, 10 HHS) 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 of black or south-east Asian ethnicity. There were more cases with type 2 diabetes (71% vs 8% p=0.005) but only one with SGLT-2 inhibitor use (postulated as a risk factor). The Covid-19 cases had more co-morbidities than controls,

increased length of stay (10 (5-22) v 1 (1-3) p=0.004) and frequently needed critical care (72% v 7% p=0.006). They had higher glucose (35 (31-43) v 25.4 (20.3-31) mmol/l, p=0.01) and higher peak sodium (148±15 v 138±3 mmol/l, p=0.03). Complications included pulmonary embolus, acute kidney injury and one case died. Monthly admission frequency was 10/month for cases and 9.6/month for controls.

Covid-19 cases with HHS had comparable gender, age and type of diabetes to control non-Covid patients, but with significantly fewer people from south-east Asian background. Biochemical markers at presentation were similar in both groups, as was overall management. There were more complications in controls, but mortality was the same at 20%. Monthly admission rate of HHS was 11/month for cases compared with 1.4/month for controls, representing a seven-fold increase.

A brief case series has also been reported,[4] but this is the first case-control study in this population. Covid-19 infection is associated with an atypical presentation of DKA with higher glucose, high sodium in older patients with co-morbidities and type 2 diabetes. HHS presents more typically but is markedly increased in frequency. Clinicians should check ketones in all patients with suspected Covid-19 infection, hyperglycaemia and acidosis and be alert to the increased frequency of HHS.

References

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

	Covid-19 positive	Control	p value
DKA	n=7	n=14	
Male (%)	6 (85%)	8 (57%)	0.2
Age (years)	52.1±13.4*	32.4±11.6*	**0.01**
Ethnicity	White 0 Black 4 (57%) Asian 3 (42%)	White 11 (78%) Black 0 Asian 3 (22%)	**<0.001** 0.1 0.14
New onset diabetes	2 (28%)	0	0.14
Type of diabetes	Type 1 diabetes 2 (28%) Type 2 Diabetes 5 (71%)	Type 1 diabetes 13 (92%) Type 2 diabetes 1 (8%)	**0.005**
Glycated haemoglobin (mmol/mol/%)	79 (65-104)/ 9.4% (8.1-11.7)	84 (73-107)/9.8% (8.8-11.9)	0.77
Prior co-morbidities	Macrovascular[a] 3 (30%) Microvascular[b] 2 (30%)	None	**0.02** 0.1
SGLT-2 inhibitor (%)	1 (14%)	0	0.33
Highest glucose (mmol/l/mg/dl)	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[∞] (%)	1 (14%)	0	0.1
Critical care admission	5 (72%)	1 (7%)	**0.006**
Complications	PE[c] 1 (14%) AKI[d] 2 (28%)	0	0.3
Length of stay (days)	10 (5-22)**	1 (1-3)**	**0.004**
Mortality (%)	1 (14%)	0	0.35
HHS	n=10	n=20	
Gender (% male)	7 (70%)	15 (75%)	0.8
Age (years)	67.6±10.5*	67 (56-79)**	0.7
Ethnicity	White 3 (30%) Black 6 (60%) Asian 1 (10%)	White 8 (40%) Black 6 (30%) Asian 6 (30%)	0.7 0.1 **0.03**

New onset Diabetes	1 (10%)	3 (15%)	0.77
Type of diabetes	Type 2 DM (100%)	Type 2 DM (100%)	1
Glycated haemoglobin (mmol/mol/%)	79 (66-85)/ 9.4% (8.2-9.9)	84 (73-107)/ 9.8% (8.8-11.9)	0.6
Prior co-morbidities	Respiratory 2 (20%) Macrovascular[a] 3 (30%) Microvascular[b] 1(10%) Neurological 0 Hypertension 8 (80%)	Respiratory 5 (25%) Macrovascular[a] 11 (55%) Microvascular[b] 4 (20%) Neurological 2 (10%) Hypertension 9 (45%)	0.8 0.2 0.6 0.1 0.08
SGLT-2 inhibitor (%)	0	0	
Highest glucose (mmol/l/mg/dl)	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 (mmol/l)	159 (155-164)**	154±14	0.3
Mixed DKA/HHS[Ω] (%)	4 (40%)	5 (25%)	0.43
Critical care admission	4 (40%)	15 (75%)	0.08
Complications	AKI[d] 2 (20%) CVA[e] 1 (10%)	AKI[d] 8 (40%) CVA[e] 4 (20%)	0.3 0.5
Length of stay	12 (10-18)**	12 (6-17)**	0.72
Mortality (%)	2 (20%)	4 (20%)	1

* mean ± Standard deviation (SD) where data is normally distributed. ** Median (Interquartile range). [a] Ischaemic heart disease, cerebrovascular disease, peripheral vascular disease [b] retinopathy, neuropathy, nephropathy [c] pulmonary embolism [d] acute kidney injury [e] cerebrovascular accident. [ᵒᵒ] Glucose ≥ 50 mmol/l [Ω] Capillary ketones ≥ 3.0 mmol/l. Univariate unadjusted analyses are shown.