Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

High prevalence of COVID-19-associated diabetic ketoacidosis in UK secondary care

Nina Goldman [a,*], Douglas Fink [b], James Cai [b], Yun-Ni Lee [c], Zoe Davies [c]

[a] Department of Respiratory Medicine, Whipps Cross University Hospital, London, UK
[b] Department of Infectious Diseases, Whipps Cross University Hospital, London, UK
[c] Department of Diabetes and Endocrinology, Whipps Cross University Hospital, London, UK

ARTICLE INFO

Article history:
Received 3 June 2020
Received in revised form
15 June 2020
Accepted 24 June 2020
Available online 29 June 2020

Keywords:
COVID-19
Type 2 diabetes mellitus
Diabetic ketoacidosis

ABSTRACT

We aim to describe the prevalence of diabetic ketoacidosis (DKA) in individuals admitted to a single centre with COVID-19. We identified 218 individuals hospitalised with COVID-19, of these four fulfilled criteria for DKA (4/218, 1.8%). We conclude DKA is common and severe in individuals hospitalised with COVID-19.

1. Introduction

Diabetes mellitus (DM), especially type 2 diabetes mellitus (T2DM), has been identified as a risk factor for poor outcomes in patients with COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], although the underlying pathophysiology is not understood [2]. Anecdotally, a high incidence of ketoacidosis has been observed in patients admitted to hospital with COVID-19 but currently there remains a lack of peer-reviewed studies addressing this [3].

Diabetic ketoacidosis (DKA) is characteristically associated with type 1 diabetes mellitus (T1DM) an autoimmune disease characterised by progressive β-cell destruction and insulin deficiency. DKA is less commonly seen in T2DM with triggers such as severe infection [4] and sodium-glucose co-transporter-2 (SGLT-2) inhibitor therapy [5].

We performed the first retrospective cross-sectional study in the UK to describe the prevalence and characteristics of DKA in patients admitted to hospital with COVID-19.

2. Method

We undertook a retrospective review of all patients with laboratory-confirmed COVID-19 admitted to a single hospital between 29th March and 6th April 2020.

All patients were screened to identify and characterise cases of DKA. DKA was defined as pH <7.3 and/or bicarbonate <15 mmol/L, blood glucose >11 mmol/L and ketonaemia ≥3.0 mmol/L [6]. Data collection encompassed demographics, drug and medical history, admission outcomes and key metabolic parameters (in particular, venous or arterial blood gas analyses, capillary blood glucose and capillary ketones).

* Corresponding author at: Whipps Cross University Hospital, Whipps Cross Road, London E11 1NR, UK.
E-mail address: nina.goldman@nhs.net (N. Goldman).
https://doi.org/10.1016/j.diabres.2020.108291
0168-8227/

3. Results

218 patients were identified who were admitted to hospital with laboratory-confirmed COVID-19 within the study period. Of these 218 patients, 61 had a pre-existing diagnosis of T2DM (61/218, 28%) and six had a pre-existing diagnosis of T1DM (6/218, 2.8%). Four of these patients fulfilled the diagnostic criteria for DKA (4/218, 1.8%). The median duration of symptoms at time of admission was 6 days for these 4 patients presenting with DKA (range 2–7 days).

Characteristics and metabolic parameters of these patients are detailed in Table 1. None of the patients with known T1DM hospitalised with confirmed COVID-19 developed DKA. Three of the four individuals presenting with DKA had a pre-existing diagnosis of T2DM and were prescribed oral hypoglycaemics: one received an SGLT2-inhibitor and another a dipeptidyl peptidase-4 (DPP-4) inhibitor. Two patients were prescribed angiotensin-converting enzyme (ACE) inhibitors. The patient who did not have known DM was found to have a high glycated haemoglobin (HbA1c) measurement on admission of 116 mmol/mol (12.8%). Mean metabolic values on admission included pH 7.18, bicarbonate 10.8 mmol/L, blood glucose 21.8 mmol/L, and capillary ketones 5.0 mmol/L.

All four patients were started on fixed rate intravenous insulin as per national guidelines [6]. All four patients had persistently elevated capillary ketones at 24 h post treatment initiation. Two patients required critical care: one for continuous venovenous haemofiltration for refractory severe metabolic acidosis and one for mechanical invasive ventilation to manage hypoxaemic respiratory failure. Two patients died and one remained in intensive care at the end of 30 days follow-up post hospitalisation.

4. Discussion

Our small retrospective cross-sectional study suggests that incidence of DKA is high in patients admitted to hospital with COVID-19. This is consistent with the hypothesis that COVID-19 predisposes individuals to DKA which may be severe and resistant to conventional therapy [7].

Prevalence of pre-existing DM (31%) was high in our population admitted with COVID-19, compared to the UK national prevalence of T2DM (7%) and the average UK hospital bed occupancy rate by individuals with T2DM (18%) [8]. This is consistent with other recent studies where T2DM has emerged as a risk factor for hospitalisation with COVID-19 [1,9].

DKA is a relatively rare complication of T2DM and often requires only short inpatient stays [10]. In contrast, DKA was present in nearly 2% of all individuals admitted to our hospital with COVID-19 and was characterised by high morbidity and mortality.

SARS-CoV-2 binds the angiotensin-converting-enzyme 2 (ACE2) receptor through its spike protein to enter cells [11,12]. ACE2 is expressed in the lung but also in other organs including on pancreatic β-cells [13]. Direct cytopathic effects of SARS-CoV-2 on pancreatic β-cell populations may contribute to this high prevalence of severe COVID-19-associated DKA in T2DM [13].

Both SARS and COVID-19 have been reported to trigger transient insulin resistance and hyperglycaemia [13,14]. SARS results in elevated glucose during admission however glucose intolerance resolved at hospital discharge [13]. This COVID-19 induced insulin resistance may explain in part poor responses to standard DKA management [7].

Although concern ACE inhibitors and angiotensin-receptor blockers (ARBs), commonly prescribed for diabetic patients, may up-regulate ACE2 expression resulting in severe COVID-19, this concern remains unfounded at present with three observational studies demonstrating no evidence of harm with ACE inhibitors or ARBs [15]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used in T2DM. Antibodies against the DPP-4 receptor has been shown to inhibit infection of cells by human CoV-EMC, the coronavirus responsible for Middle Eastern Respiratory Syndrome (MERS) [16]. Further research is required to assess whether DDP-4 inhibitors may provide therapeutic options for COVID-19 [17] and the role of intercurrent medications that might modulate virus-host interactions [13].

Limitations of our study include that we present a small dataset collected from a single centre. Necessarily, the retrospective design of our study means that some laboratory data are not available for all patients. It is likely that our study underreports the true DKA prevalence since diagnosis of DKA in our study required blood gas measurements and recording which some patients may not have received. We also did not include DKA that developed during hospital admission.

Our review highlights the need to be vigilant for DKA in patients with COVID-19. High-quality studies are required to better understand and optimise the metabolic management of COVID-19 which may be associated with severe DKA resistant to standard therapy [2]. With the scale of the COVID-19 pandemic, the longer-term impact of COVID-19 on DM also needs to be addressed.

Table 1 – Characteristics of the four patients with DKA and COVID-19.

	Age, years	Ethnicity	Known diagnosis of T1DM or T2DM	Admission metabolic parameters				
				pH	Bicarbonate, mmol/L	Glucose, mmol/L	Capillary ketones, mmol/L	HbA1c on admission, mmol/mol (NGSP %)
1	40	Asian	No	7.12	8	19	4.2	116 (12.8%)
2	42	White Other	T2DM	7.1	7.4	20	6.2	94 (10.8%)
3	59	Asian	T2DM	7.23	12	26	4.4	80 (9.5%)
4	82	Black African	T2DM	7.27	15.7	22	5.3	

CRediT authorship contribution statement

Nina Goldman: Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Douglas Fink:** Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **James Cai:** Investigation, Writing - review & editing. **Yun-Ni Lee:** Investigation, Writing - review & editing. **Zoe Davies:** Writing - review & editing.

Acknowledgements

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest: No conflicts of interest to declare.

Patients and study participants: This study was judged to be a service evaluation by Whipps Cross hospital clinical informatics department and as such no informed consent was required for study participants.

REFERENCES

[1] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054–62.

[2] Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol 2020 Apr;2:1–2.

[3] Caruso P, Longo M, Esposito K, Maiorino MI. Type 1 diabetes triggered by covid-19 pandemic: A potential outbreak?. Diabetes Res Clin Pract 2020;164:108219. https://doi.org/10.1016/j.diabres.2020.108219.

[4] Umpierrez G, Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12(4):222–32. https://doi.org/10.1038/nrendo.2016.15.

[5] Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Dia Care 2015;38(9):1638–42. https://doi.org/10.2337/dc15-1380.

[6] The Management of Diabetic Ketoacidosis in Adults [Internet]. [cited 2020 Apr 26]. Available from: http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm.

[7] Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol [Internet]; 2020 [cited 2020 Apr 28];0(0). Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213858720301522.

[8] NDIA. National Diabetes Inpatient Audit 2017. London NHS Diabetes; 2018.

[9] Zhu L, She Z-G, Cheng X, Guo J, Zhang B-H, Correspondence HL. Clinical and translational report association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab [Internet]. 2020 [cited 2020 May 31]; Available from: https://doi.org/10.1016/j.cmet.2020.04.021.

[10] Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: A retrospective cohort study. Diabetes Care 2018 Sep;41(9):1870–7.

[11] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20(6):363–74. https://doi.org/10.1038/s41577-020-0311-8.

[12] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is blocked by a clinically proven protease inhibitor. Cell 2020 Apr 16;181(2):271–280.e8.

[13] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193–9.

[14] Xue T, Li Q, Zhang Q, Lin W, Wen J, Li L, et al. Blood glucose levels in elderly subjects with type 2 diabetes during COVID-19 outbreak: a retrospective study in a single center. medRxiv. 2020 Apr 2;2020.03.31.20048579.

[15] Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB, Harrington DP. Inhibitors of the renin–angiotensin–aldosterone system and Covid-19. N Engl J Med 2020 May;1.

[16] Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013 Mar 14;495(7440):251–4.

[17] Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Research and Clinical Practice. 2020;162:108125. Elsevier Ireland Ltd; 2020.