Diabetic ketoacidosis amongst patients with COVID-19: A retrospective chart review of 220 patients in Pakistan

Asim Muhammad1 | Muhammad Hakim2 | Saima Afaq3 | Farhad Ali Khattak4 | Najmush Shakireen5 | Muhammad Jawad6 | Rabia Saeed7 | Zia Ul Haq8

1Department of Medicine, North West General Hospital, Peshawar, Pakistan
2Institute of Public Health and Social Sciences, Khyber Medical University Peshawar, Pakistan
3Department of Epidemiology and Biostatistics, Imperial College London, London, UK
4Research & Development Cell, Khyber College of Dentistry (KCD), Peshawar, Pakistan
5Department of Pulmonology, Combined Military Hospital, Peshawar, Pakistan
6Department of Family Medicine, Khyber Medical University Peshawar, Peshawar, Pakistan
7Department of Medicine, Resident Internal Medicine, North West General Hospital, Peshawar, Pakistan
8Vice Chancellor & Dean Khyber Medical University Peshawar, Peshawar, Pakistan

Correspondence
Saima Afaq, Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine, Imperial College London, London W2 1PG, UK.
Emails: safaq11@imperial.ac.uk; saima.iph@kmu.edu.pk
Farhad Ali Khattak, Research & Development Cell, Khyber College of Dentistry (KCD), Peshawar, Pakistan.
Email: farhadccd@gmail.com

Abstract
Objectives: To determine the frequency of diabetes mellitus and diabetic ketoacidosis and associated factors in COVID-19-positive patients.

Background: High mortality amongst SARS-Cov2 patients may be attributed to diabetes and diabetic ketoacidosis.

Methods: A total of 220 COVID-19 positive patients, hospitalized in North West General Hospital & Research Center, Peshawar, KP, Pakistan, from April to September 2020, were analysed using STATA 14. Patients with positive PCR were labelled as COVID-19 positive and were included in the study. Patients with a clinical picture of COVID-19 and negative PCR were excluded from the study. Those having ketonemia >0.6 and random blood glucose level >250mg/dl, while HCO3 (bicarbonate) ≤18, were labelled as diabetic ketoacidosis. The statistical significance level was set at p < .05.

Results: A total of 220 COVID-19 patients were admitted; 166 (75.4%) were male and 54 (24.5%) were female. The mean age in years of the patients was 55.95 (SD13.9). About 57.7% of patients had diabetes mellitus, and 15 (6.8%) patients developed diabetic ketoacidosis. Amongst those with DKA, 5 patients died during hospital admission. The use of steroids was significantly higher (p < .001) in the DKA group compared with non-DKA patients. Hypertension (103,46.8%) and fever (170,77.3%) were the most reported comorbidity and symptom respectively.

Conclusion: The proportion of diabetes mellitus is high in patients with COVID-19. Diabetic ketoacidosis is a frequent complication in this group associated with in-hospital mortality. Steroid administration for COVID-19 should be balanced with strict glycemic control to prevent diabetic ketoacidosis and increase hospital survival.

KEYWORDS
COVID-19, diabetes mellitus, diabetic ketoacidosis
INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a catastrophic pandemic affecting people throughout the world and severely disturbing public health security. Its pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the third identified human beta-coronavirus, which is reported to target pulmonary systems. Clinical spectrums of COVID-19 vary from asymptomatic to lethal pneumonia. Besides these, COVID-19 has unpredictable effects on many organs. However, data regarding the endocrine impact of COVID-19 are limited.

Rubino et al. proposed that SARS-CoV-2 leads to ketosis-prone diabetes via binding to its cellular entry ACE-2 receptors, which are abundant in pancreatic beta cells and adipose tissue, leading to glucose metabolism abnormalities and pancreatic beta-cell destruction. This mechanism underlies the development of diabetes mellitus (DM) in SARS-CoV2 patients. Moreover, SARS-CoV-2 may induce an autoimmune attack on the pancreatic islet cells mimicking the pathogenesis of insulin-dependent DM. The elevated HbA1C and the presence of DM risk factors in several patients may indicate that the newly diagnosed DM is a result of metabolic disturbances from COVID-19 illnesses unmasking the existing DM rather than causing the new onset of disease.

However, the unusual high incidences of diabetic ketoacidosis (DKA) in type 2 DM raise the issue of whether COVID-19 can further damage pancreatic islet cells leading to insulin deficiency states. The present study aimed to determine the frequency of DKA and diabetes mellitus in COVID-19 patients and compare the clinical characteristics and associated factors of patients with non-DKA to those with DKA.

METHODS

This retrospective chart review was carried out in the COVID-19 ward in Northwest General Hospital & Research Center Peshawar, Pakistan, which is a tertiary care hospital. Records of patients diagnosed with COVID-19, from 1 April 2020 to 30 September 2020, were obtained from the hospital. Patient records are stored on encrypted online servers and regularly updated by the on-duty doctors. Approval from Independent Ethical Committee (NWGH/2378) was obtained to access the data from the hospital server system and use it for the current research. All laboratory investigations were done during the patient admission in the hospital laboratory. Nasopharyngeal swabs were taken for confirmation of SARS COV-2 through PCR. Patients with positive PCR were labelled as COVID-19 positive and were included in the study. Clinically suspected COVID-19 patients with negative PCR while those who had positive PCR but refused in-hospital treatment were excluded. Patients with a history of diabetes, with a confirmed physician’s diagnosis, or who were on a specific diet and/or were already taking oral hypoglycemic or insulin, were labelled as previously known diabetes, while patients with no history of diabetes before admission and had HbA1c of equal to or more than 6.5% done during this admission were labelled as previously unknown diabetes. Patients with all three of the following were labelled as diabetic ketoacidosis (DKA).

1. Ketonemia >0.6
2. Random blood glucose level >250 mg/dl
3. HCO3 (bicarbonate) ≤18

Data were analysed using STATA 14. Continuous variables are presented as mean (SD) while categorical variables as percentages and numbers. Frequencies of demographic characteristics, symptoms and comorbidities were described and compared between the survivors and non-survivors using the chi-squared and Fisher’s exact test. The statistical significance level was set at p < .05 (two-sided).

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the patients. A total of 220 patients were diagnosed with COVID-19 and admitted to the NWGH between 1 April and 30 September 2020, and their data were analysed. Amongst them, 166 (75.4%) were male and 54 (24.5%) were female. The mean age in years of the patients was 55.9 (SD 13.90), while 88 (40%) patients were in the age category 56–72 years. The mean duration of stay at the hospital (in days) was 7.83 (SD 7.3). The mean duration of symptoms in days was 7.9 (SD 5.44) with approximately 78% of the patients recovering from symptoms within 10 days.

Of 220 COVID-19 diagnosed patients, 52 (23.6%) died during hospital admission. The proportion of previously known and previously unknown diabetics was 39.1% and 18.6% respectively. We identified 15 (6.8%) patients with DKA, based on the biochemical levels of ketones, blood glucose and HCO3 (bicarbonate). The mean age of those newly diagnosed with DKA was identified as 57.7 (SD12.0) (Figure 1). Hypertension was the most reported comorbidity in 103 (46.8%) patients, and amongst different symptoms, fever was the most reported in 170 (77.3%). Regarding clinical management, a total of 46 (20.9%) patients were treated in ICU. Tocilizumab and steroid were received by 89 (40.4%) and 80 (36.4%) patients respectively.

A total of 15 (6.8%) COVID-19 patients were diagnosed with DKA. Amongst these, 10 (66.7%) were males and 5 (33.3%) were females. Out of the 15 DKA patients, 9 were aged above 55 years while 6 were less than 55 years of age. The number of DKA patients who died and recovered was 5 (33.3%) and 10 (66.7%) respectively. Regarding the status of diabetes mellitus of DKA patients, 11(73.3%) had previously known diabetes and 4 (26.6%) had previously unknown diabetes. (Table 2).

Diabetic Ketoacidosis patients with hypertension was present in 5 (33.3%) patients and a similar number required management in ICU. The proportion of DKA patients who received steroids (86.7%) was significantly higher (p < .001) than that of non-DKA patients (32.7%). There were no significant differences in other demographic
DISCUSSION

The objective of our study was to determine the frequency of COVID-19 patients having DKA and compare the clinical characteristics and associated factors of patients with DKA to those without DKA. Our results show that most of the participants were males, and a major proportion was aged above 56 years while the mean length of the hospital was ~8 days. Amongst the total 220 COVID-19 patients, almost 6.82% was newly diagnosed, whereas almost 26.6% was previously known patients of diabetes mellitus. Hypertension was the most common comorbidity overall as well as amongst the patients with DKA. Comparison of biochemical and inflammatory
parameters between patients with DKA and those without DKA showed that HbA1c, ketones, blood glucose and urea were higher in the former. In contrast, HCO3 and HB levels were lower in patients with DKA compared to patients without DKA while the other biochemical markers and all inflammatory markers were similar between the two groups. The mortality in non-DKA was 22.1% while in DKA is high, 33.4%.

There is a greater risk for the previously unknown diabetes mellitus suffering from COVID-19. Diabetic ketoacidosis is a lethal complication of severe COVID-19 with poor prognostic outcomes. In our study, 6.9% was diagnosed with DKA, and many of them were unaware of their diabetes mellitus status. A case report by Nadine E Palermo found a 53 years woman who presented to the emergency department in Boston with elevated biochemical cytokines, but she...
had no diabetes-related complications before her admission and was started IV insulin with the supportive treatment of ketoacidosis.\(^\text{17}\)

The reason whether COVID-19 can damage pancreatic islet cells, leading to insulin deficiency, disturbed glucose homeostasis, inflammation, altered immune status and activation of renin–angiotensin–aldosterone system.\(^\text{12}\)

In our study, hypertension was the most reported comorbidity amongst all. A meta-analysis by Bianca de Almeida-Pititto showed that OR was 2.98 for an association of hypertension with COVID-19 infection through random effect model.\(^\text{18}\) Similarly, a study conducted by Sun et al showed hypertension was associated with an increased risk of severe COVID-19 infection.\(^\text{18,19}\) Along with high HbA1c in patients with DKA, ketones, blood glucose, urea and Hb levels were deranged, compared to normal reference values, in our study. A similar study by Juyi Li found that patients with diabetic ketosis developed acidosis, amongst whom 26.7% died.\(^\text{20}\) This suggests that COVID-19 infection caused ketosis or ketoacidosis while induced diabetic ketoacidosis for those with diabetes. Likewise, ketosis leads to the length of hospital stay and mortality.\(^\text{21}\) In our study, the mean length of the hospital was eight days. The results of this study showed that the mortality rate in non-DKA patients was 22.9%, while in patients with DKA, it was 33.3%. Furthermore, in a study conducted in Saudi Arabia, 4 patients were recovered and discharged to their homes and 1 had a complicated course and died,\(^\text{22}\) which is contradictory to our result.

The strengths of our study are: (i) no previous study has been conducted on this topic in Pakistan and (ii) the biochemical and inflammatory markers were done for all the patients. However, this study was conducted in a single private tertiary care hospital; therefore, caution may be taken before generalizing the results for other populations. Moreover, due to the system constraints, arterial blood gases were not done for all the patients.

5 | CONCLUSIONS

COVID-19 likely unmasked existing undiagnosed diabetes by provoking its metabolic complications. Both diabetes and DKA affect COVID-19 outcomes and aggravate mortality. Those diagnosed with DKA were mostly ignorant of their diabetes status. The interrelationship between diabetes and COVID-19 should prompt more research to understand the extent to which specific mechanisms of the virus might add to the deteriorating glycemic control and, in some cases, to the striking development of diabetic ketoacidosis. More research is necessary to investigate the causal relationship between diabetes, DKA and COVID-19.

ACKNOWLEDGEMENT
None.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
Asim Muhammad: Conceptualization (equal); Data curation (equal); Software (lead). Muhammad Hakim: Formal analysis (lead); Investigation (equal); Writing – original draft (equal). Saima Afaf: Formal analysis (equal); Writing – original draft (equal). Farhad Ali Khattak: Formal analysis (equal); Writing – original draft (equal). Najmush Shakireen: Data curation (equal); Investigation (equal). Muhammad Jawad: Data curation (equal); Project administration (equal). Rabia Saeed: Data curation (equal); Investigation (equal). Zia Ul Haq: Project administration (equal); Writing – review & editing (equal).

ETHICAL APPROVAL
The study was approved by the ethical committee of Northwest General Hospital Peshawar, Khyber Pakhtunkhwa, Pakistan. (NWGH/2378).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available in the supplementary material of this article.

ORCID
Saima Afaf https://orcid.org/0000-0002-9080-2220
Farhad Ali Khattak https://orcid.org/0000-0002-5933-270X

REFERENCES
1. Poudel K, Subedi P. Impact of COVID-19 pandemic on socio-economic and mental health aspects in Nepal. Int J Soc Psychiatry. 2020;66(8):748-755. doi:10.1177/0020764020942247
2. Hakim M, Khattak FA, Muhammad S, et al. Access and use experience of personal protective equipment among frontline health-care workers in Pakistan during the COVID-19 emergency: a cross-sectional study. Heal Secur. 2020;19(2):140-149. doi:10.1089/hs.2020.0142
3. Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. Int J Antimicrob Agents. 2020;56(2):106054. doi:10.1016/j.ijantimicag.2020.106054
4. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of immune response during SARS-CoV-2 infection: lessons from the past. Front Immunol. 2020;11:1949.
5. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269. doi:10.1038/s41586-020-0808-3
6. Rubin F, Amiel SA, Zimmert P, et al. New-onset diabetes in COVID-19. N Engl J Med. 2020;383(8):789-790. doi:10.1056/NEJMc2018688
7. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193-199. doi:10.1007/s00592-009-1094-4
8. 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. doi:10.1016/j.diabres.2020.108219
9. Alguwailah AM, Al-Soﬁani ME, Megdad M, et al. Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study. Cardiovasc Diabetol. 2020;19(1):205. doi:10.1186/s12933-020-01184-4
10. Landstra CP, de Koning EJP. COVID-19 and diabetes: understanding the interrelationship and risks for a severe course. Front Endocrinol. 2021;12:599.
11. Sathish T, Cao Y, Kapoor N. Newly diagnosed diabetes in COVID-19 patients. *Prim Care Diabetes*. 2021;15(1):194. doi:10.1016/j.pcd.2020.08.014
12. Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol*. 2021;17(1):11-30. doi:10.1038/s41574-020-00435-4
13. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. *J Med Virol*. 2021;93(2):1150-1153. doi:10.1002/jmv.26339
14. Knight G, Ward JD, Wardle EN. Diabetic ketoacidosis. *Lancet*. 1986;328(8518):1284-1285. doi:10.1016/S0140-6736(86)92716-9
15. The Lancet Diabetes & Endocrinology. COVID-19 and diabetes: a co-conspiracy? *Lancet Diabetes Endocrinol*. 2020;8(10):801. doi:10.1016/S2213-8587(20)30315-6
16. Batista DV, de Vieira CAF, Costa TA, Lima EG. COVID-19-associated euglycemic diabetic ketoacidosis in a patient with type 2 diabetes on SGLT2 inhibitor: a case report. *Diabetol Int*. 2021;12(3):313-316. doi:10.1007/s13340-020-00473-3
17. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. *J Clin Endocrinol Metab*. 2020;105(8):2819-2829. doi:10.1210/clinem/dgaa360
18. de Almeida-Pititto B, Dualib PM, Zaidenberg L, et al. Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr*. 2020;12(1):75. doi:10.1186/s13098-020-00586-4
19. Tadic M, Cuspidi C. The influence of diabetes and hypertension on outcome in COVID-19 patients: do we mix apples and oranges? *J Clin Hypertens*. 2021;23(2):235-237. doi:10.1111/jch.14145
20. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes, Obes Metab*. 2020;22(10):1935-1941. doi:10.1111/dom.14057
21. Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health care utilization and burden of diabetic ketoacidosis in the U.S. Over the past decade: a nationwide analysis. *Diabetes Care*. 2018;41(8):1631-1638. doi:10.2337/dc17-1379
22. Alsadhan I, Alruwashid S, Alhamad M, et al. Diabetic ketoacidosis precipitated by Coronavirus disease 2019 infection: case series. *Curr Ther Res*. 2020;93:100609. doi:10.1016/j.curtheres.2020.100609

How to cite this article: Muhammad A, Hakim M, Afaq S, et al. Diabetic ketoacidosis amongst patients with COVID-19: A retrospective chart review of 220 patients in Pakistan. *Endocrinol Diab Metab*. 2022;5:e00331. doi:10.1002/edm2.331