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# COVID-19 and Combined Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Nonketotic Coma: Report of 11 Cases

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**Abstract**

We report 11 cases of combined diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar nonketotic coma (HHNK) in coronavirus 2019 patients who presented to our institution in New Jersey, USA. The median age was 47 years (range 12-88 years). Out of the 11 patients, 7 were male and 4 were female. Out of 11 patients, 8 had type 2 diabetes mellitus (DM), 2 had undiagnosed DM, and 1 had type 1 DM. Presenting complaints included altered mental status, weakness, shortness of breath, cough, fever, vomiting, abdominal pain, chest pain, and foot pain. Out of 11 patients, pneumonia was diagnosed at presentation in 8 patients, while in 3 patients, chest X-ray was clear. Median value of initial glucose on presentation was 974 mg/dL (range 549-1556 mg/dL), and hemoglobin A1c on presentation was 13.8%. The median value of anion gap was 34 mEq/L. Out of the 11 patients, ketonemia was moderate in 6 patients, large in 3, and small in 2 patients. Acute kidney injury (AKI) occurred in 9 patients and 2 patients required renal replacement therapy. Out of the 11 patients, 6 required mechanical ventilation and 7 patients died. All the 6 patients requiring mechanical ventilation died. Our case series shows COVID-19 infection can precipitate acute metabolic complications in known DM patients or as first manifestation in undiagnosed DM patients. Patients can present with DKA/HHNK symptoms and/or respiratory symptoms. Mechanical ventilation is a poor prognostic factor. Further studies are needed to characterize prognostic factors associated with mortality in this vulnerable patient population.

**Keywords**

COVID-19, SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2, diabetes mellitus, diabetic ketoacidosis, DKA, hyperglycemic crisis, hyperglycemic hyperosmolar nonketotic coma

## Introduction

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS COV-2) and was declared a pandemic by the World Health Organization on March 11, 2020. COVID-19 most commonly affects the respiratory system, although it can also result in several extrapulmonary manifestations. These include thromboembolic, cardiovascular, and neurological complications.

## Methods

We report 11 cases of combined diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar nonketotic coma (HHNK) in COVID-19 patients who presented to our institution in New Jersey, USA. COVID-19 was diagnosed by real-time reverse-transcription polymerase chain reaction (PCR) assay. Diabetes mellitus (DM) was defined as glycated hemoglobin (HbA1c) $\geq$6.5% (48 mmol/mol) or already established diagnosis prior to the current admission. Criteria for combined DKA and HHNK on admission was pH $<$7.3, bicarbonate $<$18 mEq/L, glucose $>$250 mg/dL, anion gap $>$10 mEq/L, and ketonemia with effective serum osmolality $>$299 mOsm/kg. The electronic medical records of the 11 patients were reviewed and data on patients' age, sex, ethnicity, medical history, body mass

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index, various laboratory values, HbA1c, oral antidiabetic agents, insulin, mechanical ventilation, treatment drugs for COVID-19, and clinical outcome were collected.

## Results

Pertinent salient features are summarized in Table 1.

The median age was 47 years (range 12-88 years). Out of the 11 patients, 7 were males and 4 were females. Ethnicity distribution in our patients was as follows: 6 were Hispanic, 2 African American, 2 White, and 1 Middle Eastern descent. Comorbidities of the patients were hypertension, dyslipidemia, asthma, anxiety, depression, coronary artery disease, and gout. Out of the 11 patients, 8 had type 2 DM, 2 had undiagnosed DM, and 1 had type 1 DM. Presenting complaints included altered mental status, weakness, SOB, cough, fever, vomiting, abdominal pain, chest pain, and foot pain. Out of the 11 patients, pneumonia was diagnosed at presentation in 8 patients, while in 3 patients, chest X-ray was clear. Only 2 patients had BMI in the obesity range (more than 30). Bicarbonate 10 mEq/L in all the patients except one (14 mEq/L). One patient was taking SGLT 2 inhibitor, which is known to increase the risk of ketoacidosis. Median value of initial glucose on presentation was 974 mg/dL (range 549-1556 mg/dL) and for HbA1c on presentation was 13.8%. The median value of anion gap was 34 mEq/L. Out of 11 patients, ketonemia was moderate in 6 patients, large in 3, and small in 2 patients. All the patients received standard treatment protocol for combined DKA and HHNK with intravenous insulin infusion and intravenous fluids. Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and ferritin) elevated in all patients except one. D-dimer was elevated in all the 11 patients. Acute kidney injury occurred in 9 patients, and 2 patients required renal replacement therapy. Transaminases were elevated in 2 patients only. Out of the 11 patients, 6 required mechanical ventilation and 7 patients died. All the 6 patients requiring mechanical ventilation died.

## Discussion

Analysis of 5700 patients hospitalized with COVID-19 in the New York City area, the most common comorbidities noted were hypertension, obesity, and diabetes.[1] In a meta-analysis, DM has been associated with severe COVID-19, disease progression, acute respiratory distress syndrome development, and mortality in patients with COVID-19.[2] Pal et al report a mortality rate approaching 50% in the setting of DKA with COVID-19.[3] COVID-19 can precipitate severe manifestations of DM, including DKA and HHNK.[4] Limited literature is available regarding COVID-19 and combined DKA/HHNK. A recent systematic review of literature reported only 19 patients and emphasized differentiating isolated DKA from combined DKA and HHNK as latter tends to have higher mortality than DKA alone.[3] Goldman et al report a prevalence of 1.8% of patients admitted for COVID-19 presented with DKA.[5]

Higher levels of inflammation-related biomarkers in DM patients compared with non-DM patients has been noted.[6] In the Zhu et al study of 952 COVID-19 patients with preexisting type 2 diabetes, poor glycemic control was associated with increased need for medical interventions, multi-organ injuries, and higher mortality as compared with well-controlled glycemic control patients.[7] A significant increase in DKA at diabetes diagnosis has been noted during the COVID-19 period in 2020 as compared with the 2 previous years (44.7% in 2020 vs 24.5% in 2019 vs 24.1% in 2018).[8] A New York study reported mortality of 50% in COVID-19 patients with DKA on admission or developed during their hospital course.[9] Health care providers should target optimal glycemic control in patients with DM especially during the COVID-19 pandemic; however, Palermo et al note the unique concerns and complications of DKA with COVID-19 given the need to prevent transmission, reducing health care worker exposure, and preserving protective personal equipment and offer suggestions on using subcutaneous insulin for management.[10]

The pathological mechanisms precipitating acute metabolic complications (DKA/HHNK) in DM patients with COVID-19 is not fully understood at present. Angiotensin-converting enzyme 2 (ACE2) serves as a functional receptor for SARS-CoV-2 and is expressed in multiple tissues (alveolar cells, myocardial cells, endocrine tissues of the pancreas, proximal tubule cells of the kidney, esophagus, ileum epithelial cells, and bladder urothelial cells).[11,12] SARS-CoV-2 could cause direct damage to the pancreatic tissue leading to acute hyperglycemia. Suwanwongse et al reported 3 cases of newly diagnosed diabetes and DKA in patient with COVID-19 and propose that COVID-19 unmasked existing diabetes by aggravating its metabolic complications.[13]

## Conclusion

Our case series shows that COVID-19 infection can precipitate acute metabolic complications in known DM patients or as first manifestation in undiagnosed DM patients and is associated with substantial mortality. Patients can present with DKS/HHNK symptoms and/or respiratory symptoms. Effective communication with a health care provider and proper patient and family members education during the illness can prevent the acute metabolic complications of DM. Further studies are needed to characterize prognostic factors associated with mortality in this vulnerable patient population. Health care providers should be aware of this life-threatening complication of COVID-19 so that appropriate interventions can be done.

**Table 1.** Showing pertinent clinical characterstics and laboratory values.

| Variable[a] | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age/sex | 47/Male | 79/Female | 45/Male | 51/Male | 52/Male | 35/Female | 88/Female | 43/Male | 19/Male | 12/Male | 79/Female |
| Ethnicity | African American | Hispanic | Hispanic | White | Hispanic | Hispanic | White | Hispanic | Hispanic | African American | Middle Eastern |
| Medical history | DM | DM, HTN | DM | DM, HTN | None | HTN, DM, asthma, depression, anxiety | CAD, DM, HTN, DLD | DM, HTN, DLD, gout | DM | None | DM, HTN, DLD |
| Type 1 DM or type 2 DM or undiagnosed | Type 2 DM | Type 2 DM | Type 2 DM | Type 2 DM | Undiagnosed | Type 2 DM | Type 2 DM | Type 2 DM | Type 1 DM | Undiagnosed | Type 2 DM |
| Duration of DM | NR | NR | NR | Diagnosed within 3 months | Newly diagnosed DM | >15 years | NR | NR | NR | Newly diagnosed DM | NR |
| Hx of prior DKA/HHNK | NR | NR | NR | NR | NR | Multiple episodes | NR | NR | NR | NR | NR |
| Presenting sign and symptoms | Altered mental status | SOB, altered mental status | Altered mental status | Altered mental status, SOB, weakness | SOB, cough, weight loss | SOB, vomiting | Altered mental status | SOB, right foot pain, chest pain | Altered mental status | Vomiting, abdominal pain, altered mental status | SOB |
| Pneumonia present on admission | Positive | Positive | Positive | Positive | Positive | Positive | Negative | Positive | Negative | Negative | Positive |
| Home DM medications | Insulin sulfonylurea, | Insulin meds NR | Insulin, meds NR | NR | NA | Insulin, Metformin | Metformin, sitagliptin | Metformin, sulfonylurea, SGLT2 inhibitors | Insulin | None | Sulfonylurea metformin sitagliptin |
| BMI | 36.54 | 25.28 | 22.04 | 25.71 | 24.38 | 27.5 | 34.38 | 29.3 | 17.7 | 23.43 | 26.5 |
| HbA1c (%) | 14.6 | ND | ND | ND | ND | 13.3 | 18.3 | ND | 14.4 | 13 | 8.4 |
| pH | 6.97 | 7.13 | 6.8 | 7.16 | 6.9 | 7.1 | 7.22 | 6.96 | 7.01 | 6.81 | 7.22 |
| Bicarbonate (mEq/L) | 5 | 14 | 3 | 10 | 4 | 5 | 14 | 10 | 4 | 2 | 6 |
| Glucose on presentation (mg/dL) | 1095 | 974 | 881 | 1092 | 552 | 610 | 1284 | 948 | 1556 | 1385 | 549 |
| Serum ketones | Moderate | Moderate | Moderate | Moderate | Large | Large | Small | Small | Moderate | Large | Moderate |
| Anion gap (mEq/L) | 42 | 31 | 34 | 37 | 36 | 35 | 29 | 27 | 42 | 34 | 30 |
| Effective osmolarity (mOsm/kg) | 322.83 | 352.11 | 306.94 | 362.67 | 348 | 308 | 351.33 | 303 | 340.44 | 357 | 302.5 |
| White cell count (K/mm$^3$) | 12.2 | 20.5 | 27.0 | 23.5 | 18.3 | 11.1 | 11.8 | 16.4 | 22.5 | 21.0 | 10 |
| Hemoglobin (g/dL) | 15.2 | 13.4 | 15.8 | 16.3 | 15.6 | 12.9 | 15.8 | 17.7 | 9.1 | 15.8 | 14.7 |
| Platelets (K/mm$^3$) | 182 | 341 | 416 | 476 | 378 | 304 | 421 | 484 | 248 | 404 | 291 |
| Troponin (ng/mL) | 1.251 | 0.223 | 0.427 | 3.535 | 0.1 | 0.01 | 0.5 | 7.2 | 0.01 | 1.403 | 0.022 |
| Sodium (mEq/L) | 131 | 149 | 129 | 151 | 159 | 137 | 140 | 125 | 127 | 140 | 136 |
| Potassium (mEq/L) | 5.1 | 6.0 | 6.7 | 6.1 | 4.6 | 4.8 | 6.3 | 5.8 | 7.5 | 2.3 | 4.0 |
| Chloride (mEq/L) | 84 | 104 | 92 | 104 | 119 | 97 | 97 | 88 | 81 | 104 | 100 |
| Phosphorous (mg/dL) | 11.6 | 2.1 | 7.4 | 11.1 | 3.8 | 5.6 | 5.9 | 5.3 | 13.9 | 4.9 | 3.3 |
| BUN (mg/dL) | 92 | 70 | 31 | 69 | 62 | 17 | 114 | 88 | 59 | 37 | 32 |
| Creatinine (mg/dL) | 4.29 | 2.65 | 2.27 | 2.05 | 2.98 | 1.01 | 2.88 | 2.74 | 2.95 | 1.78 | 1.09 |
| AST (U/L) | 31 | 141 | 31 | 26 | 463 | 23 | 16 | 42 | 15 | 9 | 14 |
| ALT (U/L) | 21 | 101 | 6 | 27 | 85 | 32 | 15 | 39 | 12 | 8 | 14 |
| ESR (mm/h) | 103 | 108 | 21 | 64 | 83 | 41 | 107 | 19 | 7 | 36 | 54 |
| CRP (mg/L) | 128.1 | 110.1 | 316.3 | 140.8 | 403 | 126 | 70.5 | 341.1 | 9.8 | 90.4 | 306.7 |
| Ferritin (ng/mL) | 7500 | 2231 | ND | 2266 | 7345 | 259 | 342 | 7500 | 338 | 551 | 1198 |
| LDH (U/L) | 1676 | 730 | 591 | 736 | 640 | 461 | 277 | 718 | 187 | 434 | 1286 |
| D-dimer (μg/mL) | 13.59 | 10.22 | 2.36 | 20 | 20 | 2.35 | 1.8 | 20 | 1.55 | 6.37 | 20 |
| Fibrinogen (mg/dL) | 572 | ND | ND | ND | ND | ND | ND | 853 | 276 | 335 | 715 |
| Insulin IV or SC | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV | IV |
| Acute renal replacement therapy | HD | None | None | None | None | None | None | HD | None | None | None |
| Intubated | Yes | No | Yes | Yes | Yes | No | No | Yes | No | No | Yes |
| Treatment of COVID-19 | HCQ, azithromycin, cefepime | HCQ, azithromycin, ceftriaxone | HCQ, azithromycin | Ceftriaxone, doxycycline | HCQ, azithromycin | HCQ, ceftriaxone | HCQ, cefepime | HCQ, azithromycin, ceftriaxone | HCQ | HCQ, ceftriaxone | HCQ, azithromycin, ceftriaxone |
| Outcome | Died | Died | Died | Died | Died | Discharged | Discharged | Died | Discharged | Discharged | Died |

Abbreviations: DM, diabetes mellitus; undiagnosed, first time diagnosed with diabetes; HTN, hypertension; CAD, coronary artery disease; DLD, dyslipidemia; NR, not reported; DKA, diabetic ketoacidosis; HHNK, hyperosmolar nonketotic coma; SOB, shortness of breath; NA, not applicable; SGLT2, sodium glucose cotransporter 2 inhibitor; BMI, body mass index; HbA1c, hemoglobin A1c; ND, not done; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; IV, intravenous; SC, subcutaneous; HD, hemodialysis; HCQ, hydroxychloroquine.

[a]Reference ranges: hemoglobin A1c 4% to 6 %, pH 7.36 to 7.44, bicarbonate 21 to 31 mEq/L, glucose 70 to 110 mg/dL, anion gap 3 to 10 mEq/L, effective osmolarity 283 to 299 mOsm/kg, leucocytes 4.5 to 11 K/mm$^3$, hemoglobin 12 to 16 g/dL, platelets 140 to 440 K/mm$^3$, troponin less than 0.03 ng/mL, sodium 135 to 145 mEq/L, potassium 3.5 to 5 mEq/L, chloride 98 to 107 mEq/L, phosphorus 2.5 to 5 mg/dL, BUN 7 to 23 mg/dL, creatinine 0.6 to 1.30 mg/dL, AST 13 to 39 U/L, ALT 7 to 52 U/L, ESR 0 to 10 mm/h, CRP <10 mg/L, ferritin 12 to 300 ng/mL, LDH 140 to 271 U/L, D-dimer <0.5 (μg/mL), fibrinogen 183 to 503 mg/dL.

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## Ethics Approval

Ethical approval to report this case series was obtained from Saint Joseph's University Medical Center Review Board EX#2020-29.

## Informed consent

Verbal informed consent was obtained from the patients or legally authorized representatives (case by case) for their anonymized information to be published in this article.

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