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.

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Original Article

Assessment of Insulin Infusion Requirements in COVID-19-Infected Patients With Diabetic Ketoacidosis

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ABSTRACT

Background/Objective: Coronavirus disease 2019 (COVID-19) is thought to contribute to diabetic ketoacidosis (DKA) and worse outcomes in patients with diabetes. This study compared the cumulative insulin dose required to achieve DKA resolution in the intensive care unit among patients with type 2 diabetes and COVID-19 infection versus without COVID-19 infection.

Methods: This retrospective cohort study evaluated 100 patients—50 patients with COVID-19 in cohort 1 and 50 patients without COVID-19 in cohort 2—treated with insulin infusions for DKA at a tertiary care teaching hospital. The primary outcome was to compare the cumulative insulin dose required to achieve DKA resolution in each cohort. The secondary outcomes included time to DKA resolution, mean insulin infusion rate, and mean weight-based cumulative insulin infusion dose required to achieve DKA resolution. All endpoints were adjusted for confounders.

Results: The mean cumulative insulin dose was 190.3 units in cohort 1 versus 116.4 units in cohort 2 ($P = .0038$). Patients receiving steroids had a mean time to DKA resolution of 35.9 hours in cohort 1 versus 15.6 hours in cohort 2 ($P = .0014$). In cohort 1 versus cohort 2, the mean insulin infusion rate was 7.1 units/hour versus 5.3 units/hour ($P = .0025$), whereas the mean weight-based cumulative insulin infusion dose was 2.1 units/kg versus 1.5 units/kg ($P = .0437$), respectively.

Conclusion: COVID-19-infected patients required a significantly larger cumulative insulin dose, longer time to DKA resolution, higher insulin infusion rate, and higher weight-based insulin infusion dose to achieve DKA resolution versus non–COVID-19-infected patients with type 2 diabetes.

Introduction

In March 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a global pandemic.[1] Among patients with severe COVID-19 infection, diabetes is one of the most common underlying conditions.[2] Some studies have suggested that diabetes does not increase the risk of contracting COVID-19, although patients with diabetes have a worse prognosis with the disease, including an increased risk of intensive care unit (ICU) admission and mortality.[3,4]

Severe acute respiratory syndrome coronavirus 2 binds to angiotensin-converting enzyme 2 receptors, which are expressed in pancreatic tissue and beta cells that produce insulin. The impairment in beta cell function and insulin secretion caused by the virus in addition to the cytokine storm and amplified counterregulatory hormonal responses by the body may result in the development of diabetic ketoacidosis (DKA) and new-onset diabetes.[3] DKA is a severe metabolic disorder characterized by the buildup of ketones and acidosis. Although DKA is more common in patients with type 1 diabetes, those with type 2 diabetes may also

Abbreviations: AG, anion gap; ANOVA, analysis of variance; BG, blood glucose; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; ICU, intensive care unit; LIJMC, Long Island Jewish Medical Center; LOS, length of stay.

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develop ketoacidosis. Precipitating factors include illnesses such as infection or myocardial infarction, omission of or inadequate insulin, or newly diagnosed diabetes.[5]

Pasquel et al[6] analyzed 5029 patients from 175 U.S. hospitals and examined insulin requirements in patients with and without COVID-19 infection who were also being treated for DKA. COVID-19-infected patients required a significantly higher mean insulin infusion rate and longer time to DKA resolution than patients without COVID-19 infection. Our study aimed to assess whether a difference in insulin requirements between patients with and without COVID-19 infection being treated for DKA still exists once potential confounders, such as steroid use, are controlled for. In addition, this study aimed to aid in the growing but currently limited literature relating to diabetes, COVID-19, and DKA.

Highlights

- Coronavirus disease 2019 (COVID-19) may contribute to diabetic ketoacidosis (DKA) in type 2 diabetes
- Patients with COVID-19 and DKA have higher insulin requirements than those not infected
- Steroid use may result in a longer time to DKA resolution in patients with COVID-19
- Further research is needed to establish the link between COVID-19 and DKA

Clinical Relevance

The findings of this study strongly suggest that COVID-19-infected patients with DKA have higher insulin requirements than non-COVID-19-infected patients and that steroid use is associated with a longer time to DKA resolution in patients with COVID-19.

Methods

Study Design

This was a retrospective, single-center, cohort study that was deemed exempt by the institutional review board and was performed at Long Island Jewish Medical Center (LIJMC), a 583-bed tertiary care teaching hospital that expanded to over 800 beds during the spring 2020 surge of COVID-19. Informed consent was not required because this was a retrospective study. LIJMC was located at the epicenter of the COVID-19 pandemic, and with over 2500 COVID-related hospitalizations from March through mid-June of 2020, it had the second highest number of COVID-19 hospitalizations in New York City.[7] A total of 100 patients with DKA were included in this study with 50 patients in cohort 1 and 50 patients in cohort 2. Cohort 1 included patients with a diagnosis of COVID-19 infection who were admitted from March 1, 2020, to June 30, 2020. Cohort 2 included patients without COVID-19 infection who were admitted from January 1, 2019, to December 31, 2019. Different time periods were selected for cohorts 1 and 2 because most patients with DKA who were admitted to LIJMC during 2020 had COVID-19. In addition, the results of this research would not be influenced by seasonal changes because the DKA protocol at the institution has remained unchanged during the study period.

Study Population

Patients were included if they were 18 years or older with a history of or new diagnosis of type 2 diabetes and were being treated with a continuous insulin infusion for DKA in an ICU setting at LIJMC. Patients were excluded from this study if they had type 1 diabetes, were ruled out for COVID-19 in cohort 1, were pregnant, were not managed with an insulin infusion, were managed for DKA outside of the ICU setting, or were on an insulin infusion for reasons other than DKA.

Clinical Outcomes

The primary objective was to compare the cumulative insulin dose (ie, insulin infusion dose plus initial insulin bolus dose administered prior to insulin infusion plus additional insulin administered during insulin infusion [if applicable]) required to achieve DKA resolution in the ICU among patients with type 2 diabetes and COVID-19 infection versus those without COVID-19 infection. The use of an insulin bolus dose prior to insulin infusion was primarily based on provider preference at the institution. In addition, although rare, there were several instances where additional insulin was found to be administered outside of the insulin infusion and was included in the cumulative insulin dose calculations as this insulin may have contributed to DKA resolution. The secondary objectives were to compare the following: (1) time to DKA resolution (hours), (2) mean insulin infusion rate (units/hour), (3) mean weight-based cumulative insulin infusion dose (units/kg), and (4) mean weight-based insulin infusion rate (units/kg/hour) needed to achieve DKA resolution. The safety endpoints included the occurrence of hypoglycemia (blood glucose [BG] level, <70 mg/dL) or severe hypoglycemia (BG level, <54 mg/dL) during and up to 1 hour after the insulin infusion ended.

Data Collection

Data were collected through a retrospective chart review using electronic medical records. All data were collected and managed using Research Electronic Data Capture, a password-secure health system database designed to support data collection for research studies and in which all web-based information transmission is encrypted.[8,9] Data collected included patient demographics; diabetes history; admission diagnoses; DKA laboratory results at baseline and at resolution; concomitant hyperglycemia-causing medications; medications used for COVID-19 treatment; vasopressor use; cumulative insulin dose (units); insulin infusion data, including dose (units and units/kg), rate (units/hour and units/kg/hour), and duration (hours); hypoglycemia episodes during insulin infusion; total length of stay (LOS); and mortality.

Study Definitions

DKA was defined as meeting ≥3 of the following criteria: (1) BG level of >250 mg/dL, (2) serum bicarbonate level of <15 mmol/L, (3) anion gap (AG) of >15 mmol/L, (4) pH of <7.3, or (5) positive ketonuria or ketonemia (ie, elevated beta-hydroxybutyrate level). Patients' BG was highly considered to ensure DKA diagnosis; however, DKA was defined using ≥3 of the aforementioned criteria to better align with institutional guidelines and account for the real-world setting of a pandemic, in which certain laboratory values may not have been available. DKA resolution was defined as meeting at least 2 of the following criteria: (1) BG level of ≤250 mg/dL, (2) serum bicarbonate level of ≥15 mmol/L, (3) normal AG, (4) pH of ≥7.3, or (5) negative beta-hydroxybutyrate.[10,11] To adapt the study to a real-world situation in the setting of a pandemic, the criteria for DKA diagnosis and resolution were adapted accordingly

in relation to the cutoff for the AG. This was to account for the high patient volumes and limited ICU beds, which in turn led to transitioning patients off the insulin infusion and transferring them from the ICU with higher AGs than standard practice. If the patient met the DKA resolution criteria but the AG was not resolved, the cause was assessed. The possible causes for continued AG elevation were elevated lactate, uremia or renal failure (ie, estimated glomerular filtration rate of <45 mL/minute /1.73 m^2), or starvation ketosis.[12] In terms of the safety endpoints, hypoglycemia was defined as a BG level of <70 mg/dL, whereas severe hypoglycemia was defined as a BG level of <54 mg/dL.[13]

Concomitant hyperglycemia-causing medications, such as corticosteroids, were assessed (the complete list of these medications is shown in Supplementary Table 1).[14,15] For patients receiving steroids, the mean daily steroid doses were collected and categorized as low dose, medium dose, high dose, very high dose, or pulse therapy (the full definitions of each steroid dose category is shown in Supplementary Table 2).[16]

Statistical Analyses

For each continuous baseline factor, the Mann-Whitney test was used to examine the association between cohort (COVID-19 and non–COVID-19) and that factor. For each categorical baseline factor, the chi-square test (or Fisher exact test, as appropriate), was used to examine the association between cohort and that factor.

Analysis of variance (ANOVA) was used to examine the association between COVID-19 infection and each primary and secondary outcome. Possible confounders (including steroid use, norepinephrine use, and the use of other hyperglycemia-causing medications) were identified prior, and all endpoints were adjusted for these possible confounders. The interaction of each of these factors with cohort was included in each model. If the interaction between the confounder and cohort was significant, pairwise comparisons of the cohorts were carried out within the ANOVA model. For these comparisons, a Bonferroni adjustment was used such that a P value of <.0125 was considered statistically significant. Interactions that were not significant were removed from the model. For all outcomes, the log transformation was used to better meet the assumptions of the ANOVA model. Summary statistics are given as adjusted least squares means and their associated 95% confidence intervals (CIs) calculated from the ANOVA model on the log scale, and they are then transformed back to the original scale of measurement. Four subjects died prior to DKA resolution. Therefore, additional analyses using survival methods were carried out for the outcomes: time to resolution of DKA (hours), cumulative insulin dose (units), and mean weight-based cumulative insulin infusion dose (units/kg). Specifically, multivariable proportional hazards models were used. Subjects who died prior to resolution of DKA were considered censored in these models. Because the results of these analyses did not differ qualitatively from those of the ANOVA models, only the results of the ANOVA models are presented—both for ease of interpretation and for consistency with the analyses of the mean insulin infusion rate (units/hour) and mean weight-based insulin infusion rate (units/kg/hour). The association between hypoglycemia and cohort was examined using the chi-square test. The association between severe hypoglycemia and cohort was examined using the Fisher exact test. A P value of <.05 was considered statistically significant unless otherwise noted.

Hospital LOS was estimated using the Kaplan-Meier product limit method and compared using the log-rank test. Subjects who died in the hospital were considered censored. Summary statistics are given as median LOS with the associated 95% CI.

Results

Patient Characteristics

A total of 340 patients were identified and screened—94 patients from the cohort 1 time period and 246 patients from the cohort 2 time period. After screening patients, 240 were excluded—44 patients from cohort 1 and 196 patients from cohort 2 with the most common reason for exclusion being the use of an insulin infusion for reasons other than DKA. This left a total of 100 patients who were included in this study with 50 patients in each cohort (Fig. 1). There were 21 patients receiving steroids in cohort 1 compared with 5 patients receiving steroids in cohort 2 (Fig. 1). The mean (± standard deviation) body mass index (BMI) in cohort 1 versus cohort 2 was 32.5 (± 8.6) kg/m^2 versus 26.6 (± 9.5) kg/m^2 ($P = .0002$) (Table 1). In addition, the mean (± standard deviation) hemoglobin A1c level was 10.6% (92 mmol/mol) (± 2.6%) versus 11.8% (105 mmol/mol) (± 2.9%) in cohort 1 versus cohort 2 ($P = .0394$), respectively (Table 1). Additional baseline characteristics are shown in Table 1.

Patients' home diabetes regimens are shown in Supplementary Table 3, and the medications used to treat COVID-19 in cohort 1 and their frequencies of use are presented in Supplementary Table 4. The use of hyperglycemia-causing medications in each cohort is reported in Supplementary Table 1. Patients in cohort 1 had higher rates of loop diuretic use (44.0% vs 2.0%, $P < .0001$), norepinephrine use (62.0% vs 14.0%, $P < .0001$), and azithromycin use (28.0% vs 6.0%, $P = .0034$) than those in cohort 2. The maximum mean daily steroid dose in prednisone equivalents used prior to or during the insulin infusion is reported in Supplementary Table 2 and illustrates that the majority of patients receiving steroids in cohort 1 (61.9%) were on high-dose steroids.

Primary, Secondary, and Safety Endpoints

The adjusted mean cumulative insulin dose in cohort 1 was 190.3 units (95% CI, 148.9-243.2) versus 116.4 units (95% CI, 87.0-155.7) in cohort 2 ($P = .0038$) (Fig. 2 and Supplementary Table 5). Of the 50 patients in cohort 1, 62.0% received an initial bolus dose of insulin prior to starting the insulin infusion, whereas 34.0% of the 50 patients in cohort 2 received an initial bolus dose of insulin.

For time to DKA resolution, the interaction between steroid use and cohort was statistically significant ($P = .0286$), indicating that the association between cohort and time to DKA resolution was affected by steroid use (Table 2). For this secondary endpoint in particular, a P value of <.0125 was, therefore, considered statistically significant (Table 3). Patients receiving steroids in each cohort were, therefore, compared for this endpoint, which resulted in a mean time to DKA resolution (hours) of 35.9 (95% CI, 26.5-48.7) in cohort 1 versus 15.6 (95% CI, 8.8-27.7) in cohort 2 ($P = .0014$). In comparison, the time to DKA resolution among patients not receiving steroids in cohort 1 versus cohort 2 was 18.6 hours (95% CI, 14.7-23.6) versus 17.2 hours (95% CI, 13.8-21.4) ($P = .5902$). In addition, the time to DKA resolution in cohort 1 for patients receiving steroids versus not receiving steroids was 35.9 hours versus 18.6 hours ($P = .0005$), whereas the time to DKA resolution in cohort 2 for patients receiving steroids versus not receiving steroids was 15.6 hours versus 17.2 hours ($P = .7394$) (Table 3). No other significant interactions were found for any of the secondary endpoints.

Additional secondary endpoints were assessed and are represented in Figure 3. The mean insulin infusion rate (units/hour) was 7.1 (95% CI, 6.2-8.2) in cohort 1 versus 5.3 (95% CI, 4.5-6.3) in cohort 2 ($P = .0025$) (Fig. 3 *A* and Supplementary Table 5). Cohort 1 had a mean weight-based cumulative insulin infusion dose (units/kg) of

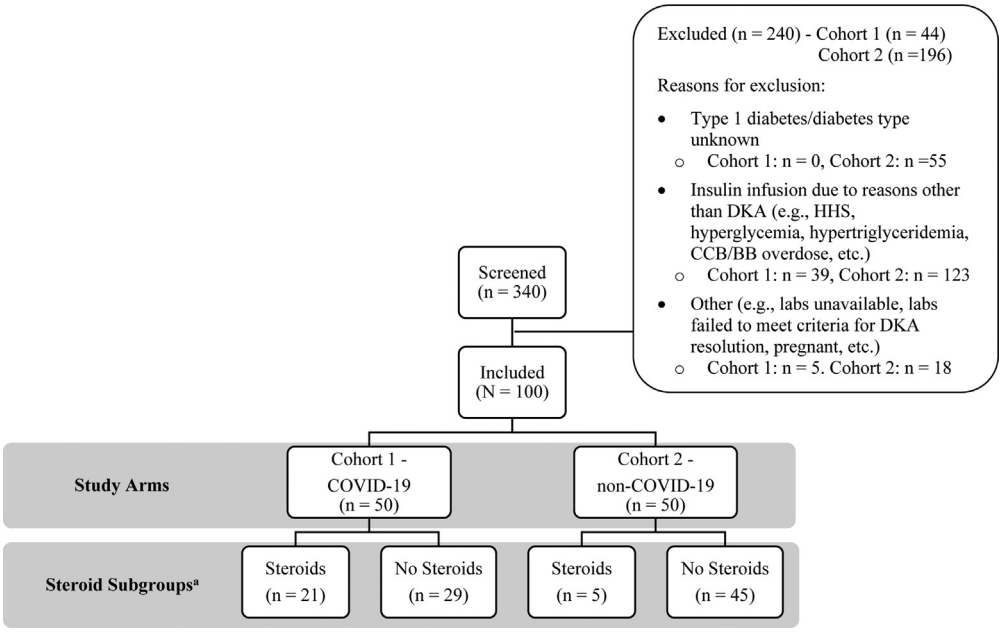

Fig. 1. Study enrollment. Flow diagram showing patient inclusion and exclusion. *BB* = beta-blocker; *CCB* = calcium channel blocker; *COVID-19* = coronavirus disease 2019; *DKA* = diabetic ketoacidosis; *HHS* = hyperglycemic hyperosmolar syndrome.
[a]Steroid use prior to or during insulin infusion.

2.1 (95% CI, 1.7-2.7) versus 1.5 (95% CI, 1.2-2.0) in cohort 2 (P = .0437) (Fig. 3 *B* and Supplementary Table 5). The mean weight-based insulin infusion rate (units/kg/hour) in cohort 1 was 0.08 (95% CI, 0.07-0.09) versus 0.07 (95% CI, 0.06-0.08) in cohort 2 (P = .2044) (Fig. 3 *C* and Supplementary Table 5).

The safety endpoints were also evaluated and demonstrated that the rate of hypoglycemia was 18% (n = 9) in cohort 1 versus 8% (n = 4) in cohort 2 (P = .1371), whereas the rate of severe hypoglycemia was 8% (n = 4) versus 2% (n = 1), respectively (P = .3622) (Supplementary Fig. 1).

Exploratory Findings

Additional findings included the total hospital LOS. The median LOS in cohort 1 was 30.0 days (95% CI, 21.0-67.0) versus 7.0 days (95% CI, 4.0-9.0) in cohort 2 (P < .0001).

Disease severity and progression were assessed using vasopressor data. Vasopressor requirements at baseline (ie, prior to or at the time that the insulin infusion was started) were used as an indicator of disease severity. Initiation of additional vasopressors during DKA treatment was interpreted as disease progression. In cohort 1, 46% of patients were on a vasopressor at baseline with 6 of these patients on ≥2 vasopressors (Table 1). Vasopressors were started or added in 30% of patients in cohort 1 while on the insulin infusion with a total of 12 of 32 patients (37.5%) requiring ≥2 vasopressors during insulin infusion use. In comparison, 8% of patients were on a vasopressor at baseline in cohort 2 with 1 patient on ≥2 vasopressors (Table 1). Vasopressors were started or added in 10% of patients in cohort 2 while being treated with the insulin infusion with a total of 3 of 7 patients (42.9%) on ≥2 vasopressors during insulin infusion use.

Disease severity and progression were also measured by assessing dialysis use and intubation at baseline and during insulin infusion. In cohort 1, 3 patients (6.0%) were on intermittent hemodialysis at baseline (ie, prior to admission) with 14% of patients initiating dialysis during insulin infusion treatment. In comparison, 2 patients (4.0%) were on intermittent hemodialysis at baseline in cohort 2, and dialysis was initiated in 4% of patients during insulin infusion treatment. At baseline (ie, prior to insulin infusion initiation), 30 patients (60.0%) were intubated in cohort 1 versus 7 patients (14.0%) in cohort 2 (P < .0001) (Table 1). During the insulin infusion, an additional 2 patients (4.0%) in cohort 1 were intubated versus 1 patient (2.0%) in cohort 2.

The mortality rate in cohort 1 was 62.0% versus 4.0% in cohort 2 (P < .0001). In cohort 1, 3 of the 31 patients who died did so before DKA resolution, whereas 1 of the 2 patients who died in cohort 2 did so before DKA resolution. DKA laboratory results at resolution are reported in Supplementary Table 6. In cohort 1, 26 of the 46 patients with an available AG achieved a normal AG at the time of resolution. Among the 20 patients who did not, 14 had an elevated lactate level or lactic acidosis, 17 had uremia or renal failure, and 1 had starvation ketosis. However, these patients met other criteria for DKA resolution. In comparison, 3 of 49 patients for whom an AG was available in cohort 2 did not achieve a normal AG at DKA resolution. Of these patients, 2 had a mixture of an elevated lactate level and uremia, whereas 1 experienced only uremia.

Discussion

COVID-19-infected patients with type 2 diabetes required a significantly larger cumulative insulin dose, longer time to DKA resolution, higher insulin infusion rate, and higher weight-based cumulative insulin infusion dose to achieve DKA resolution than non–COVID-19-infected patients. No significant difference was observed in the weight-based insulin infusion rate (units/kg/hour) or incidence of hypoglycemia events between the 2 cohorts, although a larger number of hypoglycemia and severe hypoglycemia events occurred in cohort 1 than in cohort 2. Corticosteroid use was associated with a significantly longer time to DKA resolution in the COVID-19 cohort without influencing the results of the other endpoints. Our study supports the findings of Pasquel et al[6] and provides additional data on admission diagnoses, race, disease severity markers, and concurrent hyperglycemia-causing

Table 1
Baseline Characteristics

Characteristic	Cohort 1: COVID-19 (N = 50)	Cohort 2: non–COVID-19 (N = 50)	*P* value
Age, y—mean ± SD	60.0 ± 13.5	60.4 ± 13.2	.8146
Sex, male—n (%)	30 (60.0)	26 (52.0)	.4203
Race—n (%)			.1620
Caucasian	8 (16.0)	13 (26.0)	
African American	29 (58.0)	21 (42.0)	
Asian	6 (12.0)	3 (6.0)	
Other or unknown	7 (14.0)	13 (26.0)	
Ethnicity—n (%)			.3649
Hispanic or Latino	3 (6.0)	1 (2.0)	
Not Hispanic or Latino	47 (94.0)	47 (94.0)	
Unknown	0 (0.0)	2 (4.0)	
BMI, kg/m^2—mean ± SD[a]	32.5 ± 8.6	26.6 ± 9.5	.0002
BMI, kg/m^2—n (%)			<.0001
Underweight/normal weight (<25)	7 (14.0)	28 (56.0)	
Overweight (25-29.9)	14 (28.0)	10 (20.0)	
Obese (≥30)	24 (48.0)	12 (24.0)	
Unknown BMI	5 (10.0)	0 (0.0)	
Baseline laboratory tests[b]			
Triglycerides—mean ± SD	308.7 ± 202.7	158.9 ± 67.8	.0387
pH—mean ± SD	7.17 ± 0.09	7.2 ± 0.1	.1329
Serum bicarbonate—mean ± SD	14.5 ± 5.2	12.7 ± 5.6	.1217
Urine ketones—n (%)			.0010
Positive	21 (42.0)	37 (74.0)	…
Negative	3 (6.0)	4 (8.0)	…
Unknown	26 (52.0)	9 (18.0)	…
BHB—mean ± SD	5.5 ± 3.8	7.0 ± 3.6	.0774
Anion gap—mean ± SD	24.6 ± 6.8	27.2 ± 7.0	.0456
Blood glucose—mean ± SD	487.1 ± 200.2	544.5 ± 198.2	.1135
HbA1c, % (mmol/mol)—mean ± SD	10.6 (92) ± 2.6	11.8 (105) ± 2.9	.0394
Serum creatinine on the day of ICU admission—mean ± SD	2.5 ± 3.1	2.0 ± 1.7	.6791
Diabetes history—n (%)			.7596
Yes	44 (88.0)	43 (86.0)	…
No/new onset	5 (10.0)	7 (14.0)	…
Unknown	1 (2.0)	0 (0.0)	…
DKA history—n (%)			.1722
Yes	3 (6.0)	5 (10.0)	…
No	9 (18.0)	16 (32.0)	…
Unknown	38 (76.0)	29 (58.0)	…
IHD prior to admission—n (%)	3 (6.0)	2 (4.0)	1.0000
Intubated prior to insulin infusion—n (%)	30 (60.0)	7 (14.0)	<.0001
Primary diagnosis—n (%)			
COVID-19	42 (84.0)	0 (0.0)	<.0001
Non–COVID-19-related infection	0 (0.0)	10 (20.0)	.0009
Cardiovascular event	2 (4.0)	2 (4.0)	1.0000
Non–COVID-19/non–infectious-related respiratory diagnosis	0 (0.0)	2 (4.0)	.4949
Diabetes-related diagnosis (ie, DKA)	13 (26.0)	40 (80.0)	<.0001
Altered mental status	2 (4.0)	3 (6.0)	1.0000
Other	0 (0.0)	2 (4.0)	.4949
Hospital day admitted to the ICU—median (25th percentile, 75th percentile)	2.0 (1.0, 3.0)	1.0 (1.0, 1.0)	…
Vasopressor use at baseline[c], yes—n (%)	23 (46.0)	4 (8.0)	<.0001
1 vasopressor	17 (34.0)	3 (6.0)	…
≥2 vasopressors	6 (12.0)	1 (2.0)	…
Endocrine consult, yes—n (%)	18 (36.0)	40 (80.0)	<.0001
Time of endocrine consult—n (%)			
Before insulin infusion	4 (8.0)	0 (0.0)	…
During insulin infusion	9 (18.0)	14 (28.0)	…
After insulin infusion	5 (10.0)	26 (52.0)	…

Abbreviations: BHB = beta-hydroxybutyrate; BMI = body mass index; COVID-19 = coronavirus disease 2019; DKA = diabetic ketoacidosis; HbA1c = hemoglobin A1c; ICU = intensive care unit; IHD = intermittent hemodialysis; SD = standard deviation.

[a] BMI reported based on available values (cohort 1, n = 45; cohort 2, n = 50).

[b] Baseline laboratory results reported based on available values. Unless otherwise noted here, n = 50 for baseline laboratory results for each cohort (cohort 1, triglycerides, n = 18; pH, n = 47; BHB, n = 31; and HbA1c, n = 48, and cohort 2, triglycerides, n = 11; BHB, n = 46; and HbA1c, n = 49).

[c] Vasopressor use at baseline signifies the use of vasopressors prior to or at the time that the insulin infusion was initiated.

medications and COVID-19 therapies, such as corticosteroid use, which were missing in their study.

The baseline characteristics in our study demonstrate that patients in cohort 1 had a significantly higher BMI and lower hemoglobin A1c level than those in cohort 2. Most patients in cohorts 1 and 2 were male with the majority of patients with COVID-19 in cohort 1 being African American and having a history of type 2 diabetes mellitus. This aligns with the demographic data portrayed by previous studies, such as those cited in the study by Pasquel et al[6] and in a systematic literature review by Pal et al.[17] Because BMI was significantly higher in cohort 1 than in cohort 2 and a higher BMI may contribute to greater insulin resistance, it would

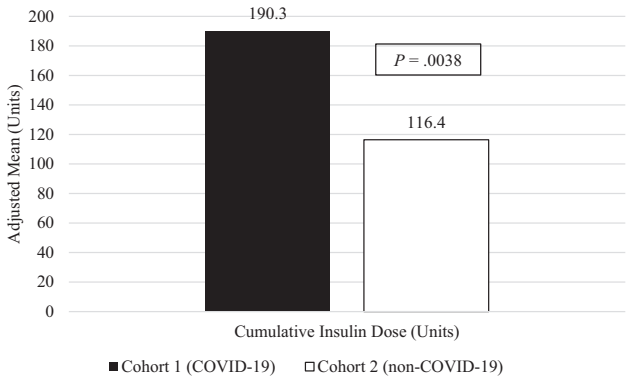

Fig. 2. Primary endpoint. Adjusted mean cumulative insulin dose (units) required to achieve diabetic ketoacidosis resolution in cohort 1 compared with that in cohort 2. *COVID-19* = coronavirus disease 2019.

have been preferable to include BMI as a possible confounder in the multivariable models. Ten percent of patients in cohort 1 were missing BMI data, which is likely associated with higher severity of illness; it was not appropriate to include BMI in any of the multivariable analyses considering that the missing information was not missing at random and was only missing from 1 cohort.

An additional difference noted between the 2 cohorts was the number of endocrine consults completed as cohort 2 had a significantly higher number of endocrine consults than cohort 1. Endocrine consults at the institution are usually completed close to the time that patients are transferred out of the ICU, as denoted in Table 1 by the majority of consults being completed after the insulin infusion in cohort 2. Owing to the high rates of mortality in cohort 1, several patients did not approach being transferred out of the ICU and, therefore, did not receive an endocrine consult.

Based on our exploratory findings, clinical outcomes were found to be more adverse in cohort 1 than in cohort 2. This was represented by higher rates of mortality and a longer median hospital LOS in the COVID-19 cohort. Previous studies reported DKA mortality in COVID-19 around 45.0%, whereas our study reports in-hospital mortality of 62.0%.[17] This could be due to the small sample size and time frame of our study (ie, prior to the use of dexamethasone 6 mg in patients with COVID-19).[18] Disease severity and disease progression were also worse in the COVID-19 cohort as represented by vasopressor data, dialysis use, and intubation rates. Mechanically ventilated patients with COVID-19 and DKA have been shown to have worse outcomes, whereas patients with diabetes have also been shown to have longer lengths of stay than patients without diabetes according to previously published case reports.[19]

The limitations of our study include its design as a retrospective chart review completed during a global pandemic where there was deviation from standard documentation, staffing limitations, different staffing ratios, and travel nurses who were not familiar with the electronic medical record or hospital protocols and had to be familiarized with both. Although the DKA protocol had remained unchanged during the study period, real-world implementation may have varied in the setting of a pandemic although the intent of this study was not to assess adherence to the institution's DKA protocol. Furthermore, an additional limitation may be the variability that exists between cohorts 1 and 2. Given the limited number of patients with DKA and without COVID-19 during the time period used for cohort 1, patients in cohorts 1 and 2 were selected from different time periods, and therefore, patients in cohort 1 were treated during the initial surge of the pandemic where variability in treatment may have occurred, whereas patients in cohort 2 were not. In addition, patients in cohort 2 were not as severely ill as those in cohort 1. Finding a comparator group

Table 2
Interaction Between Cohort and Steroid Use

Outcome	Cohort	Steroids		*P* value for interaction[a]
		Yes	No	
		Adjusted mean (95% confidence interval)	Adjusted mean (95% confidence interval)	
Cumulative insulin dose (units)	COVID-19	286.4 (200.2-409.6)	129.7 (98.1-171.3)	.0941
	Non–COVID-19	98.2 (50.0-192.8)	87.2 (67.3-113.1)	
Time to DKA resolution (h)	COVID-19	35.9 (26.5-48.7)	18.6 (14.7-23.6)	.0286
	Non–COVID-19	15.6 (8.8-27.7)	17.2 (13.8-21.4)	
Mean insulin infusion rate (units/h)	COVID-19	7.6 (6.1-9.4)	6.7 (5.7-7.9)	.6305
	Non–COVID-19	6.2 (4.2-9.2)	4.9 (4.2-5.7)	
Mean weight-based cumulative insulin infusion dose (units/kg)	COVID-19	3.0 (2.1-4.3)	1.5 (1.2-2.0)	.0982
	Non–COVID-19	1.3 (0.7-2.4)	1.2 (0.9-1.6)	
Mean weight-based insulin infusion rate (units/kg/h)	COVID-19	0.08 (0.06-0.1)	0.08 (0.07-0.09)	.5507
	Non–COVID-19	0.08 (0.05-0.1)	0.07 (0.06-0.08)	

Abbreviations: COVID-19 = coronavirus disease 2019; DKA = diabetic ketoacidosis.
[a] *P* value of <.05 was considered statistically significant.

Table 3
Secondary Endpoint—Time to DKA Resolution (Hours)

Outcome	Cohort	Steroid use	No steroid use	*P* value[a]
		Hours—adjusted mean (95% confidence interval)	Hours—adjusted mean (95% confidence interval)	
Time to DKA resolution (h)	Cohort 1 (COVID-19)	35.9 (26.5-48.7)	18.6 (14.7-23.6)	.0005
	Cohort 2 (non–COVID-19)	15.6 (8.8-27.7)	17.2 (13.8-21.4)	.7394
	***P* value**[a]	.0014	.5902	

Abbreviations: COVID-19 = coronavirus disease 2019; DKA = diabetic ketoacidosis.
[a] *P* value of <.0125 was considered statistically significant.

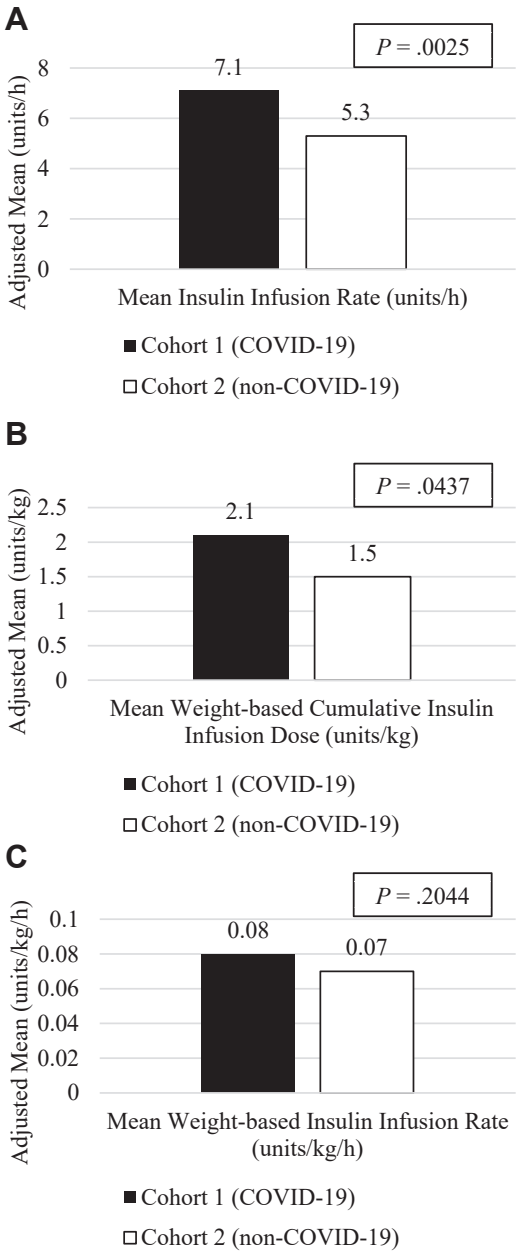

Fig. 3. Additional secondary endpoints. Mean insulin infusion rate (units/hour), weight-based cumulative insulin infusion dose (units/kg), and weight-based insulin infusion rate (units/kg/hour) required to achieve diabetic ketoacidosis resolution in cohort 1 compared with that in cohort 2. *COVID-19* = coronavirus disease 2019.

with comparable disease severity, however, was not feasible given the typical non–COVID-19-infected patients who present with DKA. The mortality rate in cohort 2, signifying disease severity, is similar to the expected DKA mortality rate in patients without COVID-19.[6] The small sample size used in the study, particularly the small sample of patients on steroids, is an additional limitation because the time period used in this study was prior to steroids becoming the standard of care for COVID-19 treatment and, typically, non–COVID-19-infected patients with DKA are not on steroids unless required due to underlying disease processes.[18] Another limitation is that this study was conducted prior to the availability of COVID-19 vaccines and before it was known that there is no evidence to support the use of other tried therapies (eg, hydroxychloroquine and azithromycin). Confounders, such as the use of concurrent hyperglycemia-causing medications, were also present although these were controlled for.

Conclusion

Our findings strongly suggest that patients with COVID-19 and DKA have higher insulin requirements than patients without COVID-19 infection and propose that institutions should consider adjusting DKA treatment protocols for patients with COVID-19 infection. Recommendations include highlighting that patients with COVID-19 and type 2 diabetes may require higher cumulative insulin doses and, if on high-dose steroids, longer time to achieve DKA resolution. The results of this study further suggest that additional research is needed to establish the link between COVID-19, diabetes, and DKA. Areas for further investigation include studies with larger samples of patients receiving steroids, patients with type 1 diabetes, and patients who have been vaccinated against COVID-19.

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Author Contributions

D.F., C.A.G., K.P.F., R.S.R, T.C., A.T., and N.K. contributed to the development of the study design; C.A.G. is responsible for the conception of the study question, which was tailored by D.F., K.P.F, R.S.R., and T.C; D.F., C.A.G., and K.P.F. participated in data collection; D.F. wrote the manuscript; D.F., C.A.G., K.P.F., R.S.R, T.C., A.T., and N.K. reviewed and edited the manuscript; N.K. conducted the statistical analyses; D.F., C.A.G., K.P.F., R.S.R, T.C., A.T., and N.K are the guarantors of this work and take responsibility for the integrity of the data.

Disclosure

The authors have no multiplicity of interest to disclose.

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