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Clinical Characteristics of Dkain Patients with COVID-19 Infection: A Case Series

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Abstract

Diabetes Mellitus (DM) is one of the comorbidities that can increase the mortality rate of COVID-19 patients. The characteristics of patients who present with Diabetic Ketoacidosis (DKA) and COVID-19 co morbidity have not been reviewed sufficiently. In this study, we describe 7 patients admitted to our department with impression of DKA and concomitant COVID-19. Patients' lab data, imaging and outcomes were documented in full detail. While DKA is a common presentation following an infectious etiology in COVID-19 comorbidity, we observed that DKA presented with atypical symptoms and divergent outcomes. As a result, we suggest that more advanced studies with larger sample size should be conducted to investigate detailed DKA characteristics, managements and outcomes to revise the management protocol of DKA in COVID-19 infection.

Keywords: Diabetic ketoacidosis; COVID-19

Abbreviations

M: Male; F: Female; Rec: Recovered; Exp: Expired; WBC: White Blood Cell; PCO2: Partial Pressure of Carbon Dioxide; HCO3: Bicarbonate; BUN: Blood Urea Nitrogen; Na: Sodium; K: Potassium; Ca: Calcium; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; BS: Blood Sugar; LDH: Lactate Dehydrogenase

Introduction

After a short time from the initial COVID-19 outbreak towards the end of 2019 in China, the world announced a global pandemic in March 2020; consequently, great attention was paid to people with comorbidities such as diabetes, and metabolic and cardiovascular diseases because of severe complications and poor outcomes in the groups with COVID-19 infection [1,2].

Also, the mortality rate from COVID-19 in these individuals is significantly higher than the average population [3]. Diabetes mellitus contributes to increasing comorbidity and mortality in patients with severe COVID-19 and acute respiratory distress syndrome in comparison with the general population [4-6]. However, this risk is more significant for type 1 diabetes than type 2 [7,8]. On the other hand, COVID-19 might lead to overt diabetes in normal individuals or exacerbation of hyperglycemia in previously diabetic patients [9].

Previous studies revealed that poor glycemic control or overweight in metabolic syndrome patients could be a risk factor for severe infections through the immune response impairment to viral or bacterial infections. Central obesity and diabetes may increase pro-inflammatory cytokine secretion related to impaired immune response [10-12].

Diabetic ketoacidosis is the most common hyperglycemic crisis state in diabetic population, which increases in case of severe infections [13]. COVID-19 illness usually unmasks the prevailing DM rather than inducing new-onset diabetes. However, the unusually high incidence of DKA among COVID-19 positive patients with type 2 DM raises the issue that COVID-19 can destroy the pancreatic islet cells and promotes insulin deficiency states.

Potential diabetogenic effect of COVID-19, inappropriate serum level of insulin, could change the glucose metabolism with an increased incidence of hyperglycemia in severe COVID-19 [14,15]. Currently, there is little information about the relationship between COVID-19 and DKA. Some previous studies suggested that elevated levels of serum inflammatory factors in severe COVID-19 increased the risk of developing DKA in patients. Interlukin6 (IL6) has also been detected as a common inflammatory factor in both DKA and COVID-19. High levels of interleukin-6 in COVID-19 predispose individuals to DKA [16]. However, extended research is needed to identify the correlation between COVID-19 and diabetes acute complications such as DKA.

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Methods

This study was done on patients admitted to our department from October 28th to November 30th, 2020. Medical history, demographic characteristics, biomedical and biochemical, medical management, clinical course of hospitalization of patients, and their outcomes were documented in full detail. Real-Time (RT-PCR) test and High Resolution Computed Tomography of the lung (HRCT) were also reported and classified in this survey [17]. In all cases, HRCT severity scoring was calculated for each of the 5 lobes considering the extent of anatomic involvement, as follows: 0, no involvement; 1, <5% involvement; 2.5%-25% involvement; 3.26%-50% involvement; 4.51%-75% involvement; and 5, >75% involvement; the resulting score was the sum of each individual lobar score (0 to 25) [17]. Diabetic ketoacidosis is defined as plasma glucose >250 mg/dl, arterial Ph<7.35, and/or HCO3<18 mmol/L, and positive serum ketones. Based on diagnostic criteria and electrolyte and fluid deficits, patients are categorized into three categories of mild, moderate, and severe form of DKA [18]. All patients were managed with DKA protocol [19], including Intravenous Hydration (IV), insulin infusion, and electrolyte replacement with close monitoring. According to the protocol in Iran, management of Covid-19 is done as follows: In the first to seventh days after the onset of symptoms, only Remdesivir; on the seventh to tenth day Remdesivir + corticosteroid, and after ten days only corticosteroid were prescribed for patients. Data were expressed as number, median and percentage. However, statistical analysis could not be done due to the small sample size in this survey. All participants (themselves or their relatives) completed and signed informed consent before their participation in this study.

Case Presentation

Case 1

The first patient was a 25-year-old lady with a past medical history of hyperlipidemia and diabetes mellitus type1 (T1DM) presented to the emergency ward with nausea, vomiting, epigastric pain, and pleuritic chest pain three days before her admission. She complained of cough and fever 7 days before her recent admission; the RT-PCR test was positive for COVID-19. The clinician recommended isolation at home because of mild symptoms. She used only insulin (regular and NPH) and claimed to use them regularly. She was alert, awake, and oriented to time, place, and person. Initial vital signs showed body temperature 38.10c frontally, Blood Pressure (BP) 100/70 mmHg, Respiratory Rate (RR) 22 breaths/min, and Heart Rate (HR) 110 beats/min. Oxygen saturation was 80% in an ambient air, which increased to 92% by O2 therapy by reservoir mask. Her HRCT also showed patchy infiltration of both lungs with the score of11/25 (Figure 1). Electrocardiogram (ECG) showed normal sinus rhythm. In the initial evaluation stages, high random blood sugar (410 mg/dl) with compensated metabolic acidosis (PH: 7.28, HCO3: 14.2 mmol/L, PCO2: 31.2) in the venous blood gas was recorded for her. Both serum ketone and urine ketone were positive, so she was transferred to the ward and managed as moderate DKA. IV isotonic fluid followed by infusion of regular insulin was started, and electrolyte was closely monitored as well. Corticosteroid and prophylaxis of thrombosis were also regarded for her. After 30 hours of admission, her symptoms were relieved, acidosis improved, and blood glucose controlled. Diabetic diet was initiated for her and infusion insulin changed to subcutaneous one. She was finally discharged after five days in a fair condition.

Case 2

A 45-year-old man, prisoner, and known case of T2DM were admitted due to a history of coffee ground vomiting and generalized weakness. The patient also complained of a severe cough in the last few days. The patient's drug history was Glibenclamide which has not been used regularly in recent weeks. The BP was 120/75 mmHg with no orthostatic change, RR of 18 breaths/min, HR of 75 beats/min, and temperature of 36.20°C frontally. The oxygen saturation in the ambient air was 95% without oxygen. ECG showed sinus tachycardia. Random blood sugar was recorded 615 by both laboratory and glucometer. Mixed metabolic and respiratory acidosis was detected in his blood gas (PH: 7.25, HCO3: 6.2 mmol/L, PCO2: 27.4). Serum ketone was also positive by dilution of 1/8. The initial management of Gastrointestinal (GI) bleeding and DKA was started for him (Pantoprazole infusion, serial Hemoglobin (Hb) monitoring, and bolus IV hydration continued by regular insulin infusion). Oral levofloxacin was also started for him in the ward. Endoscopy was done for him, which showed to be normal. The radiologist reported his HRCT typical forCOVID-19. Score: 8/25 (Figure 1). RT-PCR was positive for COVID-19. His blood sugar and other lab data improved at first. Then, basal Insulin and diabetic diet were started for him after 20 hours of his initial management. However, after one day, his condition progressively worsened and DKA management was started for him again. He developed cardiac arrest on the fourth day of his admission at 2:55 AM and ultimately expired after 45 min of starting Cardiopulmonary Resuscitation (CPR).

Case 3

The third patient was a 66-year-old woman with a history of Hypertension (HTN) and T2DM for about 8 years. She referred to the hospital with a chief complaint of fever and drowsiness one day before admission. She was well till about six days before hospital admission and after that she developed with fever, chills, and dry cough. One day before admission, her symptoms were accompanied by nausea, vomiting, generalized abdominal pain, urinary incontinence, and drowsiness that progressively worsened. Her recent drug history was Empaglifazon 10 mg 2 times a day (BID) and amlodipine 5 mg BID. The patient was drowsy and disoriented. Initial vital signs showed BP of 90/60 mmhg, RR of 20 breaths/min, HR of 60 beats/min, and temperature of 36.20°C frontally. The oxygen saturation was 90% without oxygen in the ambient air and 93% with oxygen therapy. Random blood sugar was recorded 381. Her blood gas showed metabolic acidosis and respiratory acidosis (PH: 7.13, HCO3: 8.6 mmol/L, and PCO2:27.1). Both serum (by dilution of 1/16) and urine ketone were positive. Computed Tomography (CT) head was normal. ECG revealed a normal sinus rhythm. A sepsis workup was done for her, and an empirical IV antibiotic was started. Severe DKA management was initiated for her immediately (infusion of isotonic fluid, half saline, regular insulin and potassium chloride infusion with monitoring of serum electrolyte). Due to her history of chills, fever and dry cough, and high prevalence of COVID-19, HRCT was done for her. Score: 11/25 (Figure 1). RT-PCR also confirmed COVID-19 infection. Remdesiver also started. Her condition improved about three days after her admission, and long-acting insulin and oral diet were started for her as soon as her level of consciousness improved. She recovered and was discharged after nine days. Her anti-glycemic drug also changed to long and short-acting insulin.

Case 4

A 64- year- old male with a past medical history of HTN and T2DM was referred to the hospital by a general physician due to dyspnea and decreased O2 saturation (73%). He had a history of fever, chills, generalized body pain and dyspnea starting from one week before his admission that were worsened. Due to the high possibility of COVID-19, he was first admitted to the grey zone of the emergency department. His blood pressure, HR, RR and body temperature were140/85 mmHg 21 breaths/min, 110 beats/min, and 37.10°C, respectively. Bilateral crackle was detected in lung physical exam. HRCT showed bilateral ground glass opacity in favor of severe COVID-19.Score: 22/25 (Figure 1). His blood gas analysis indicated respiratory alkalosis and metabolic acidosis (PH: 7.35, HCO3: 11 mmol/L, and PCO2:20.1). Random blood sugar was reported 240 mg/dl. Serum ketone was checked that was positive. Initial management of severeCOVID-19 and DKA was started for him. The patient's condition worsened during the period of hospitalization, and he required mechanical ventilation on the second day of hospital admission. No significant improvement was also documented in his blood sugar and VBG. He had a cardiac arrest on the third day of his admission and unfortunately expired.

Case 5

The fifth patient was a 43-year- old woman, a known case of T2DM, HTN and HLD referred by a cardiologist to our department. She complained about dizziness, dysuria, and dyspnea which started two days before her admission. She had a BP of 140/90 mmhg respiratory rate of 20 breaths/min, heart rate of 120 beats/min, and temperature of 36.20°C frontally. The oxygen saturation was recorded 92% without oxygen in the room. Her random blood sugar was 545 mg/dl. Venous blood gas was in favor of severe metabolic acidosis (PH: 6.96, HCO3: 4.9 mmol/L and PCO2: 14). Both serum and urine were positive for ketone bodies. Management of severe DKA (Isotonic saline infusion continued by regular insulin infusion+half saline and then DW5%+half saline) was started, and she was transferred to the ICU for close monitoring. Due to her complaint about dyspnea and high prevalence of COVID-19, he was tested for Covid-19. RT-PCR was positive and HRCT showed mild involvement. Score: 2/25 (Figure 1). Brain MRI was also done for her due to her dizziness which was unremarkable. Her general condition was recovered after a few days and the patient was discharged from the hospital.

Case 6

An 82-year-old male, a known case of DM, was brought to the hospital due to the decreased level of consciousness and two episodes of bloody vomiting. He had a history of diarrhea for three days, cough and malaise. Upon arrival to the hospital, he underwent mechanical ventilation due to his respiratory distress and low oxygen saturation (46%). His initial BP was 90/55 mmHg, HR: 94, body temperature 35.8°C frontally, and respiratory rate of 23 breath/min. No focal neurologic deficit was documented in his neurological physical examination. The random blood glucose was 440 mg/dl, and venous blood gas revealed approximately compensated metabolic acidosis (PH: 7.33, HCO3: 11.1 mmol/L, and PCO2: 21.7). Brain CT scan did not reveal any new ischemic or hemorrhagic event. Serum ketone was positive by dilution of 1/8. Initial management of GI bleeding (IV pantoprazole infusion, isotonic saline infusion, monitoring of blood hemoglobin, and reserve of pack cell) and moderate DKA management was started for him. His Nasogastric (NG) tube became clear after washing with 500 ccs normal saline. A broad-spectrum IV antibiotic was also administered for him due to high suspicion to septicemia. Imaging characteristics were consistent with severe COVID-19 infection with progression to ARDS with a score of 24/25 (Figure 1). Remdesivir was also started for him. Due to the history of GI bleeding, enoxaparin was not administered at the time of admission. He developed multiorgan failure and expired after three days.

Case 7

A 75-year-old male with a past medical history of DM, HTN, HLD, Ischemic Heart Disease (IHD), and Cerebrovascular Accident (CVA) was referred to the hospital by an EMC due to decreased level of consciousness and dyspnea which start done day before admission that progressively increased. His drug consumption history was Aspirin, tamsulosin, metformin, nitrocantin, piracetam, quetiapine, and amlodipine. Upon admission, he became intubated due to the altered mental status. His initial vital sign was BP 110/60 mmHg, HR82 beat/min, body temperature 36.5 frontally, and RR14 breath/min. No focal neurologic deficit was detected in the physical exam. The oxygen saturation was 83% in the room air. Evidence of hypodensity in deep white matter and periventricular area suggested chronic ischemic insult detected in the brain CT scan. HRCT showed bilateral patchy ground glass involvement in favor of COVID-19 and superimposed bacterial infection with a score of 12/25 (Figure 1). Random blood sugar was reported 615 mg/dl. Venous blood gas analysis was in favor of compensated metabolic acidosis (PH: 7.26, HCO3: 10.3 mmol/L,

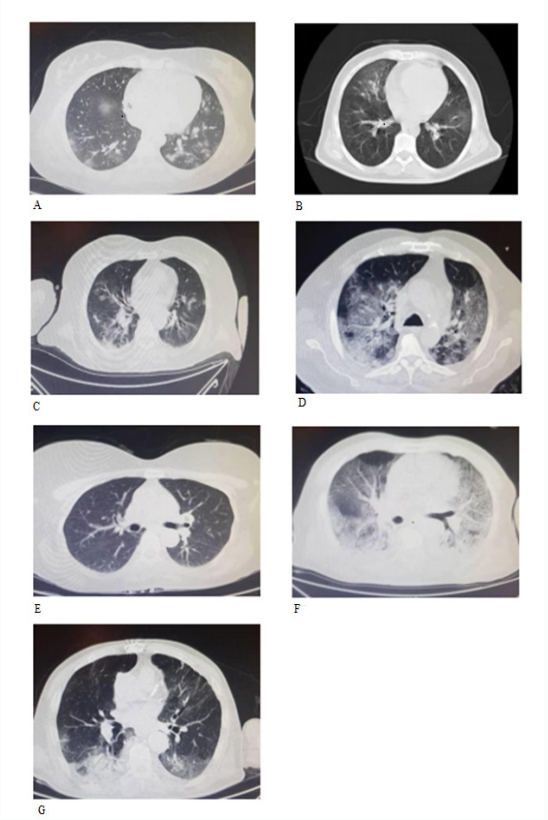

Figure 1: Chest CT finding of patients on COVID-19 and its severity score per each of the 5 lobes considering the extent of anatomic involvement: A (Case 1), score: 11/25; B, (Case 2), score:8/25 ;C (Case 3), score:11/25; D (Case 4), score:22/25; E (Case 5), score 2/25; F (Case 6), score 24/25; G (Case 7), score: 12/25.

and PCO2:22.9). Management of moderate DKA and COVID-19 was started for him. Due to the acute kidney injury (Blood Urine Nitrogen (BUN): 88mg/dL and Creatinine (CR): 4.56 mg/dL) and anuria during the hospital course, hemodialysis followed by ultra filtration was performed for him in three consecutive days. During the hospital admission, he developed GI bleeding and Hb drop, and his hemodynamic state was unstable. He received three bags of pack cell with IV infusion of pantoprazole. He ultimately expired after 6 days of mechanical ventilation.

Result

Between October 28th and November 30th, 2020, 7 (3 females and 4 males) patients were admitted to our center with the impression of DKA and COVID-19. All patients had a history of diabetes mellitus. Of the seven patients, one (14%) had a history of T1DM and 6 (76%) patients were known cases of T2DM. Demographic and laboratory data are shown in Table 1. The median age of the patients was 66 (with a range of 25 to 82 years old). The average of the initial random blood sugar and serum HCO3 was 463.71 mg/dl and 9.47 mmol/L, respectively among the patients in this survey. The majority of the patients (71%) presented with DKA symptoms rather than respiratory symptoms related to COVID-19. Four patients expired in this survey; all of them were male and 3 of them required mechanical ventilation after their admission. Two patients' lung involvement was mild, three of them had moderate involvement and imaging consisted of severe infection in the remaining two patients. Four patients presented with moderate and three with severe DKA based on DKA classification. All the four patients who expired presented with moderate DKA, one of whom had mild lung involvement, one moderate and two were in a severe category. The average of C-Reactive Protein (CRP) was >150 mg/dl in the patients who expired and 50 mg/dl in the group who recovered. Lactate dehydrogenase (LDH) averages were 813 and 640.33 in the patients who expired and recovered, respectively.

Discussion

Diabetes mellitus is one of the leading causes of severity and mortality in patients with COVID-19, with several times increase in mortality in patients [20]. More accurate glucose control has been associated with better outcomes in these patients [21]. In some studies, DKA has been reported as the first manifestation of diabetes in patients with COVID-19 [22].

In a recent survey, insulin resistance and insulin deficiency were associated with severe COVID-19 infection. In 30% of cases, it continued until recovery and they were discharged from the hospital [14]. Several theories have been proposed to create inappropriate serum insulin levels and persistent hyperglycemic state in these patients. Angiotensin Converting Enzyme2 (ACE2) is detected as a functional receptor for SARS-COV-2. The virus destroys the islet cells in the pancreas by binding to these receptors. Destruction of the residual Beta-cell can cause absolute insulin deficiency in diabetic patients with COVID-19 infection. In addition, the immune response against SARS-COV-2 may cause autoimmune attack against the pancreatic islet cell, which causes a decrease in the level of serum angoitensin2 secondary to down regulation of ACE 2 receptor and finally reduced insulin secretion [23,24]. Rubino et al. [25] recommended that SARS-COV-2 can bind to ACE-2 receptors on the pancreatic Beta-cells or adipose tissue, which could induce pancreatic Beta-cells destruction and render the patients prone to glucose metabolism disturbance or diabetic ketoacidosis. In addition, SARS-COV-2 may trigger an autoimmune process against pancreatic Beta-cells through the aberrant of innate immunity. Pancreatic Beta-cells damaged even by direct attack of SARS-COV-2 or indirectly through over activity of the immune system can elucidate COVID-19-related insulin deficiency and diabetes, something like the pathogenesis of DM 1 [23]. Insulin deficiency or insulin resistance could promote glycogen synthesis, and decrease glycogen breakdown on target organs of the liver or muscle [26]. Also, inappropriate insulin secretion or insulin resistance increases lipolysis in the adipose tissue, associated with impaired glucose tolerance, and increased serum-Free Fatty Acid (FFA) levels. FFA and adipokines secreted from adipose tissue could consequently blunt insulin signaling on the muscle tissue, stimulate gluconeogenesis by the liver, and interrupt with insulin response (Figure 2) [27, 28].

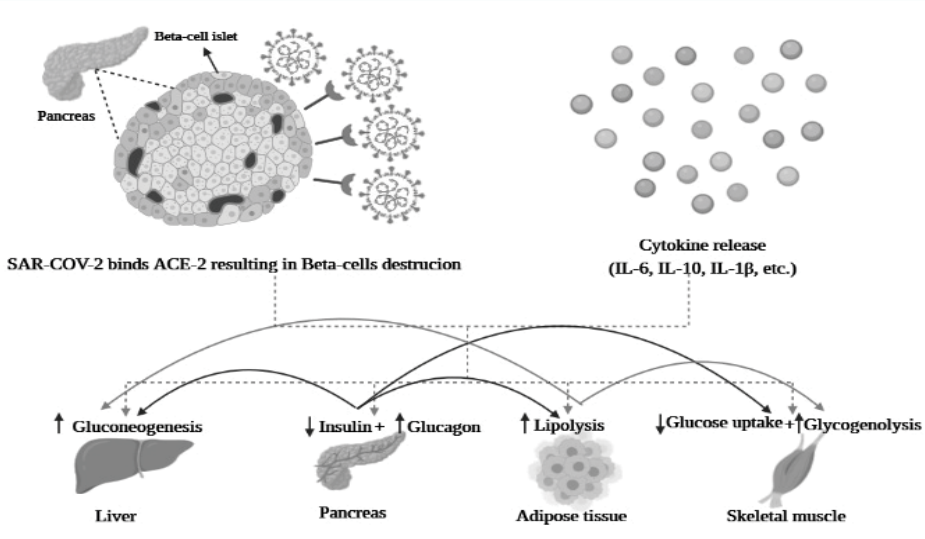

Figure 2: Covid 19 viruses can trigger hyperglycemic state by insulin deficiency or resistance and increase in counter regulatory hormones through the direct effect on ACE receptors of pancreas, liver and muscle tissue. Secondary lipolysis or insulin deficiency can additionally aggravate hyper glycemic state through stimulate gluconeogenesis or glycogenolysis.

Table 1: Demographic characteristic, laboratory data, and clinical outcome.

parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	reference range
Age	25	45	66	64	43	82	75	-
Gender	F	M	F	M	F	M	M	-
Outcome	Rec	Exp	Rec	Exp	Rec	Exp	Exp	-
WBC (×1000/mm^2)	3.2	12.8	9.5	8.5	10.6	8.1	4.8	10-Apr
Hemoglobin (g/dL)	12.4	12.4	16.6	14.4	13.1	13.3	14.5	M:14-18 F: 12-16
M.C.V (fL)	88.3	84	84.4	85.9	87.5	83.2	97.3	80-96
Platelet (×1000/mm^2)	129	221	137	298	297	221	133	150-450
pH	7.28	7.21	7.13	7.35	6.96	7.33	7.26	7.35-7.45
PCO_2(mmHg)	30	19.1	27.1	20.1	14	21.7	22.9	41-51
HCO_3(mmol/L)	14.2	7.7	8.6	11	4.9	11.1	10.3	22-28
Covid-19 PCR	Positive	Positive	Positive	-	Positive	Positive	Positive	-
BUN (mg/dL)	13	31	64	20	30	43	66	20-Aug
Creatinine (mg/dL)	1.1	1.5	2	1.58	1.63	1.67	3.56	M: 0.8-1.3 F: 0.6-1.2
Na (meq/L)	137	130	160	141	139	133	142	136-145
K (meq/L)	5.1	4.9	4.4	5.4	6	4.4	5	3.5-5.5
Ca (mg/dL)	8.6	9.1	8.6	9.8	10.1	8.9	8.7	8.6-10.3
Serum Ketone	+++	++++	++++	+++	++++	+++	++	-
Urine Ketone	+++	++	+++		++	-	-	-
Urine culture	-	No growth	Candida nonalbicans	-	No growth	No growth	-	-
Blood culture	-	No growth	No growth	-	No growth	-	No growth	-
AST (U/L)	13	9	14	40	180	159	-	M: <37 F: <31
ALT (U/L)	11	4	23	16	300	58	-	M: <41 F: <31
Alkaline phosphatase (U/L)	220	222	345	175	290	114	-	M: 64-306 F: 80-306
Total bilirubin (mg/dL)	0.3	0.3	0.4	0.4	1.3	0.7	-	0.1-1.2
Direct bilirubin (mg/dL)	0.2	0.1	0.1	0.2	0.7	0.3	-	<0.3
Total protein (g/L)	6.31	6.3	5.7	7.3	6.4	3	-	6.4-8.3
Albumin (g/L)	3.71	3.8	3.4	3.9	3.3	2.2	3.2	3.5-5.2
ESR (mm/hr)	22	55	42	-	78	-	-	M: 0-20 F: 0-30
CRP (mg/L)	29	>150	68	-	53	>150	>150	<6 negative
BS (mg/dL)	410	619	381	240	545	440	615	74-99
LDH (U/L)	702	516	509	-	710	953	970	<480

Therefore, impairment in insulin secretion from B-cell in accordance with excess inflammatory cytokine release and counter-regulatory hormonal responses could induce acute metabolic deterioration and development of severe DKA or Hyperglycemic Hyperosmolar State (HHS), resistant to conventional therapy [23,29,30].

However, further studies are needed to investigate the association between SARS-COV-2 infection and the pancreatic angiotensin system by detail.

In Li et al. [31] survey, inflammation induced by COVID-19 has been shown to cause ketoacidosis. The presence of ketone bodies in the serum and urine was associated with long-term hospitalization, more need for mechanical ventilation, acute liver injury, ARDS, and higher mortality [31]. Medication used for COVID-19 treatment is another point that must be regarded; corticosteroid and lopinavir can precipitate hyperglycemia in patients [32-34].

DKA mortality in COVID-19 patients has been reported up to 50%.In our study, four out of seven patients needed mechanical ventilation and all of them expired finally. Six patients were known cases of T2DM and one of the T1DM. Male gender and presence of comorbidities including old age, IHD and AKI were associated with high mortality rate and severity in our survey. Insulin infusion dosage was also higher than the standard dose (0.1 unit/kg). These results were consistent with previous studies [14,31].

Fluid resuscitation is a challenging issue in management of DKA in COVID-19 patients. Aggressive hydration can cause volume overload and increase the risk of ARDS. Therefore, in addition to volume replacement in patients, it is necessary to consider the volume overload at the same time, which makes DKA management difficult [9,35]. The guideline for management of DKA in COVID-19infection recommended infusion of 250cc bolus isotonic saline infusion at the first of DKA management, and the treatment should be continued based on the patient's weight and blood gas state rather than blood sugar. Acidosis is regarded as the main goal for the management of DKA in recent investigations [36]. This research was a case series cross-sectional study which investigated the clinical features and outcome of DKA in the patients with COVID-19 infection. Unfortunately, due to our small sample size, statistical analysis was not possible. More advanced studies with larger sample size are needed to investigate detailed DKA characteristics, risk factors, role of glycemic control before and during hospital admission, and DKA management and its outcome in COVID-19 infection.

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References

1. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus.

Am J Physiol Endocrinol Metab. 2020;318(5):E736-41.

2. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020;14(5):1463-5.
3. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PloS one. 2020;15(8):e0238215.
4. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract. 2020;162:108132.
5. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14(4):303-10.
6. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia-a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020;14(4):395-403.
7. McGurnaghan S, Weir A, Bishop J, Kennedy S, Blackbourn L, McAllister D, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol. 2021;9(2):82-93.
8. Al Hayek AA, Robert AA, Alotaibi ZK, Al Dawish M. Clinical characteristics of hospitalized and home isolated COVID-19 patients with type 1 diabetes. Diabetes Metab Syndr. 2020;14(6):1841-5.
9. Kuchay MS, Reddy PK, Gagneja S, Mathew A, Mishra SK. Short term follow-up of patients presenting with acute onset diabetes and diabetic ketoacidosis during an episode of COVID-19. Diabetes Metab Syndr. 2020;14(6):2039-41.
10. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes care. 2018;41(10):2127-35.
11. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes(Lond). 2013;37(3):333-40.
12. Honce R, Schultz-Cherry S. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol. 2019;10:1071.
13. Pal R, Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: a systematic review of literature. Diabetes Metab Syndr. 2020;14(6):1563-9.
14. Armeni E, Aziz U, Qamar S, Nasir C, Nethaji R, Negus R, et al. Rosenthal, Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series. Lancet Diabetes Endocrinol. 2020;8(8):660-3.
15. Wang W, Lu J, Gu W, Zhang Y, Liu J, Ning G. Care for diabetes with COVID-19: Advice from China. J Diabetes. 2020;12(5):417-9.
16. Palermo NE, Sadhu AR, McDonnell ME. Diabetic ketoacidosis in COVID-19: unique concerns and considerations. J Clin Endocrinol Metabol. 2020;105(8):2819-29.
17. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808-17.
18. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes care. 2006;29(12):2739-48.
19. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes care. 2009;32(7):1335-43.
20. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr. 2020;14(4):535-45.
21. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-77. e3.
22. Reddy PK, Kuchay MS, Mehta Y, Mishra SK. Diabetic ketoacidosis precipitated by COVID-19: a report of two cases and review of literature. Diabetes Metab Syndr. 2020;14(5):1459-62.
23. 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.
24. Hollstein T, Schulte DM, Schulz J, Glück A, Ziegler AG, Bonifacio E, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nature metabol. 2020;2(10):1021-4.
25. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-onset diabetes in Covid-19. N Engl J Med. 2020;383(8):789-90.
26. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005;26(2):19.
27. Belfort R, Mandarino L, Kashyap S, Wirfel K, Pratipanawatr T, Berria R, et al. Dose-response effect of elevated plasma free fatty acid on insulin signaling. Diabetes. 2005;54(6):1640-8.
28. Roden M, Stingl H, Chandramouli V, Schumann WC, Hofer A, Landau BR, et al. Effects of free fatty acid elevation on postabsorptive endogenous glucose production and gluconeogenesis in humans. Diabetes. 2000;49(5):701-7.
29. Muniangi-Muhitu H, Akalestou E, Salem V, Misra S, Oliver NS, Rutter GA. Covid-19 and Diabetes: A Complex Bidirectional Relationship. Front Endocrinol (Lausanne). 2020;11:582936.
30. Coate KC, Cha J, Shrestha S, Wang W, Gonçalves LM, Almaça J, et al. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. Cell Metab. 2020;32(6):1028-40.e4.
31. 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):1935-41.
32. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure?-a rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents. 2020;56(2):106080.
33. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020;162:108142.
34. Lee GA, Rao M, Mulligan K, Lo JC, Aweeka F, Schwarz JM, et al. Effects of ritonavir and amprenavir on insulin sensitivity in healthy volunteers. AIDS. 2007;21(16): 2183.
35. Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. Ann Intensive Care. 2020;10(1):1-24.
36. Rayman G, Lumb A, Kennon B, Cottrell C, Nagi D, Page E, et al. Guidance on the management of Diabetic Ketoacidosis in the exceptional circumstances of the COVID-19 pandemic. Diabet Med. 2020;37(7):1214-6.