Diabetic ketoacidosis as a feature of COVID-19 | in patients with diabetes: A case series

Cetoacidosis diabética como manifestación de COVID-19 en pacientes con diabetes: serie de casos

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ABSTRACT

Studies on diabetic ketoacidosis (DKA) in COVID-19 patients are scarce. Infections are a precipitating factor for DKA in adults with diabetes. Over a 1-week period, five patients with diabetes presented to our hospital with DKA. SARS-CoV-2 infection was diagnosed in all five cases. All patients developed acute respiratory distress syndrome and died during this hospitalization. In this case series of male patients with diabetes, reluctance to present to the hospital, severe pneumonia, high C-reactive protein (29.35 ± 14.74 mg/dl), high white cell count ($14,140 \pm 5444$ mm³), high D-dimer (2578 ± 1155 ng/ml), high lactate dehydrogenase (656 ± 249 U/L), and BMI >25 kg/m² may have contributed to their poor outcomes.

Key words: Diabetic ketoacidosis. COVID-19. Diabetes.

RESUMEN

Los estudios sobre cetoacidosis diabética (CAD) en pacientes con enfermedad por coronavirus 2019 (COVID-19) son escasos. Las infecciones son un factor desencadenante de la CAD en adultos con diabetes. Durante un periodo de una semana, cinco pacientes que viven con diabetes se presentaron en nuestro hospital con CAD. La infección por coronavirus 2 del síndrome respiratorio agudo grave (SARS-CoV-2) se diagnosticó en los cinco casos. Todos los pacientes desarrollaron síndrome de dificultad respiratoria aguda (SDRA) y murieron durante esta hospitalización. En esta serie de casos de pacientes de sexo masculino con diabetes, la renuencia a acudir al hospital, neumonía grave, proteína C reactiva alta (29.35 ± 14.74 mg/dl), recuento alto de glóbulos blancos ($14,140 \pm 5,444$ mm³), dímero D alto ($2,578 \pm 1,155$ ng/ml), deshidrogenasa láctica alta (656 ± 249 U/l) e índice de masa corporal >25 kg/m² pudieron haber contribuido a su mal pronóstico.

Palabras clave: Cetoacidosis diabética. COVID-19. Diabetes.

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INTRODUCTION

Diabetes mellitus has been shown to be a comorbidity that is associated with severe disease, acute respiratory distress syndrome (ARDS) and increased mortality in COVID-19. The coexistence of diabetes mellitus and COVID-19 is an unfortunate situation in which one disease can complicate the other. On the other hand, COVID-19 may worsen glycemic control and cause acute hyperglycemia crises among patients with preexisting diabetes or induces new-onset diabetes¹. Studies on diabetic ketoacidosis (DKA) in COVID-19 patients are scarce in Mexico. Over a 1-week period from April 21 to May 3, 2020, five patients presented with DKA that did not improve with usual treatment. Five patients with diabetes presented to the hospital with a history of fever, polydipsia, and respiratory symptoms. They delayed seeking medical care because of fear of COVID-19. On admission, they reported good treatment adherence for diabetes. DKA was diagnosed in all cases. All had no alterations on electrocardiogram, and other foci of infections were ruled out. None of the patients received steroid management during hospitalization. All patients developed ARDS and were intubated and sedated. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all five cases.

CASE PRESENTATION

Case #1

A 61-year-old man with a history of type 2 diabetes mellitus (T2DM) and regular alcohol consumption presented with a 3-day history of fever, dyspnea, cough, polydipsia, and lethargy. His examination was notable for dry mucous membranes, tachycardia, Kussmaul breathing, and a BMI of 25 kg/m². Laboratory results showed hyperglycemia (381 mg/dl) and metabolic acidosis (blood gas analysis: pH 7.23, bicarbonate 10.5 mmol/L, anion gap of 18.5, lactate 1.2 mmol/L) with ketones and glucosuria in the urine. A chest X-ray revealed bilateral ground-glass

Figure 1. Chest X-ray on admission showing bilateral ground-glass opacities with bilateral patchy shadowing.

opacities with bilateral patchy shadowing (Fig. 1). Intravenous sodium chloride 0.9% solutions and an insulin infusion (maximum infusion rate of 12 U/h) with antibiotic therapy were initiated but did not result in clinical improvement and glycemic control. He was positive for SARS-CoV-2. The patient developed ARDS and was intubated and sedated. He died 2 days after hospitalization due to acute kidney injury and shock.

Case #2

A 53-year-old man with a history of T2DM presented with a 3-day history of fever, dyspnea, polydipsia, and nausea. His examination was notable for dry mucous membranes, tachycardia, and a BMI of 33.1 kg/m². Laboratory results showed hyperglycemia (324 mg/dl) and metabolic acidosis (blood gas analysis: pH 7.25, bicarbonate 13.9 mmol/L, anion gap of 23, and lactate 0.9 mmol/L) with ketones and glucosuria in the urine. A chest X-ray revealed bilateral ground-glass opacities with bilateral infiltrates (Fig. 2). Intravenous sodium chloride 0.9% solutions, potassium replacement, and insulin infusion (maximum infusion rate of 10 U/h) with antibiotic therapy were initiated but did not result in clinical improvement and glycemic control. He tested positive for SARS-CoV-2. The patient developed ARDS which required mechanical ventilation and died 3 days after hospitalization.

Figure 2. Chest X-ray on admission showing bilateral ground-glass opacities with bilateral infiltrates.

Figure 4. Chest X-ray on admission showing bilateral ground-glass opacities.

Figure 3. Chest X-ray on admission showing bilateral ground-glass opacities with infiltrates.

Case #3

A 55-year-old man with a history of T2DM and regular alcohol consumption presented to our hospital with a 4-day history of fever, dyspnea, cough, polydipsia, headache, and lethargy. His examination was notable for dry mucous membranes, tachycardia, Kussmaul breathing, and a BMI of 38.2 kg/m². Laboratory results showed hyperglycemia (376 mg/dl), metabolic acidosis (blood gas analysis: pH 7.16, bicarbonate 6.1 mmol/L, anion gap of 27.9, and lactate 1 mmol/L),

elevated serum creatinine (3.5 mg/dl) with ketones and glucosuria in the urine. A chest X-ray revealed bilateral ground-glass opacities with infiltrates (Fig. 3). Intravenous Hartmann solutions and an insulin infusion (maximum infusion rate of 9 U/h) with antibiotic therapy were initiated but did not result in clinical improvement and glycemic control. He was positive for SARS-CoV-2. The patient developed ARDS and was intubated and sedated. He died 2 days after hospitalization.

Case #4

A 40-year-old man with a history of T2DM presented with a 1-week history of fever, dyspnea, polydipsia, and sore throat. His examination was notable for dry mucous membranes, tachycardia, Kussmaul breathing, and a BMI of 26 kg/m². On admission, the laboratory results showed hyperglycemia (273 mg/dl) and metabolic acidosis (blood gas analysis: pH 7.20, bicarbonate 10.8 mmol/L, anion gap of 27.2, and lactate 0.8 mmol/L) with ketones and glucosuria in the urine. A chest X-ray revealed bilateral ground-glass opacities (Fig. 4). Intravenous sodium chloride 0.9% solutions, potassium replacement, and insulin infusion (maximum infusion rate of 14 U/h) with antibiotic therapy were initiated but did not result

in clinical improvement and glycemic control. He tested positive for SARS-CoV-2 and developed ARDS, which required mechanical ventilation. The patient died 9 days after hospitalization.

Case #5

A 55-year-old man with a history of T2DM presented with a 1-week history of fever, dyspnea, polydipsia, cough, headache, and lethargy. His examination was notable for dry mucous membranes, tachycardia, and a BMI of 29.7 kg/m². On admission, laboratory results showed hyperglycemia (354 mg/dl) and metabolic acidosis (blood gas analysis: pH 7.26, bicarbonate 13 mmol/L, anion gap of 18, and lactate 1.1 mmol/L) with ketones and glucosuria in the urine. A chest X-ray revealed bilateral ground-glass opacities (Fig. 5). Intravenous sodium chloride 0.9% solutions, potassium replacement, and insulin infusion (maximum infusion rate of 11 U/h) with antibiotic therapy were initiated but did not result in clinical improvement and glycemic control. He tested positive for SARS-CoV-2. The patient developed ARDS and was intubated and sedated. He died 8 days after hospitalization.

All the patients clinical characteristics are summarized in Table 1.

DISCUSSION

DKA is the most common acute hyperglycemic emergency in people with diabetes mellitus. DKA occurs mostly in people with uncontrolled type 1 diabetes mellitus (T1DM) but also occurs in adults with poorly controlled T2DM who are under stressful conditions, such as acute medical or surgical illnesses. Although any illness or physiological stress can precipitate DKA, the most frequent causes are infections, particularly urinary tract infections and gastroenteritis. In developed countries, the risk of death resulting from DKA is <1% in adults, whereas in developing countries, the DKA mortality is much higher. Among adults, DKA-related deaths occur primarily in older persons (>60 years of age) and in those with severe precipitating illnesses².

Figure 5. Chest X-ray on admission showing bilateral ground-glass opacities.

By way of comparison, our service had treated only 1-2 DKA patients every week over the previous year, usually caused by urinary tract infections and new-onset diabetes mellitus, with no mortalities.

COVID-19 and diabetes

A retrospective study reported that the incidence of DKA in hospitalized patients with diabetes and COVID-19 was 20%, but the study was limited because of the small number of patients³. New-onset diabetes and severe complications of preexisting diabetes have been observed in patients with COVID-19^{4,5}.

Diabetes is a frequently reported comorbidity in COVID-19 patients. Diabetes and obesity are risk factors for severe and critical forms of COVID-19 requiring the use of invasive mechanical ventilation, with high mortality rates. COVID-19 is usually associated with poor glycemic control and a high risk of ketoacidosis in people with diabetes. The characteristics of people with diabetes who are at risk for developing severe and critical forms of COVID-19 are still under investigation⁶.

Emerging evidence demonstrates an important direct mechanistic link between metabolic/endocrine systems and the viral disease process. A possible mechanism of damage to the beta cell would be

different from the one observed in the context of T1DM, as it would be linked to the action of enteroviruses and coxsackievirus as modulators of an immune response that ends up causing loss of beta-cell function. However, little information exists on whether coronaviruses affect the beta cell in this way⁷.

In a report of 4 autopsies of patients who died of SARS (caused by SARS-CoV-1), the pancreas specimens from 3 of 4 of the patients showed the presence of SARS-CoV-1 viral particles in 1-24% of the cells by immunohistochemistry, showing that other betacoronaviruses can infect the human pancreas⁸. More recently, Yao et al.⁹ reported the presence of SARS-CoV-2 in the pancreatic tissue of a patient at autopsy.

This presence of coronavirus in endocrine pancreas cells would explain what was observed during the SARS-CoV-1 epidemic: people with nondiabetes who never had been treated with corticosteroids presented hyperglycemia during hospitalization. In the same group of patients over a 3-year follow-up, only 5% of these patients maintained a diabetic status¹⁰. From these data, it can be inferred that SARS-CoV-2 damage to beta cells is temporary and is associated with blunt insulin production or secretion.

The interactions between SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) might provide another mechanism of the pathophysiology of DKA in COVID-19 patients. Angiotensin-converting enzyme 2 (ACE2), a key enzyme in the RAAS, is encoded by a gene on chromosome Xp22¹¹. ACE2 catalyzes the conversion of angiotensin II (Ang II) to angiotensin 1-7, which protects against the deleterious circulatory effects of Ang II. ACE2 is highly expressed in the lungs, heart, vasculature, kidney, gut, and pancreas and serves as the entry point for SARS-CoV-2. In the human pancreas, ACE2 is highly expressed in endocrine tissue, providing an entry point for SARS-CoV-2.

After endocytosis of the virus complex, ACE2 expression is downregulated, and the destruction of ACE2 is upregulated by a surface protein called disintegrin and metalloproteinase 17 (ADAM17), which is activated by 3 simultaneous mechanisms: excess Ang II, endocytosed SARS-CoV-2 spike proteins, and tumor necrosis factor receptor,

leading to a disbalance of the RAAS with more Ang II¹¹. The excess of Ang II in the pancreas generates local vasoconstriction, which affects the first phase of insulin secretion, and this secretory mechanism could also be affected by the intracellular action of Ang II¹².

Two factors might contribute to the acute worsening of pancreatic beta-cell function and precipitate DKA: (1) entry of SARS-CoV-2 into pancreatic islet cells may directly aggravate beta-cell injury^{10,13} and (2) downregulation and destruction of ACE2 after viral entry can lead to unopposed angiotensin II effects, which may temporarily impede insulin secretion¹².

The relationship between SARS-CoV-2 and the RAAS can complicate DKA management. Excessive fluid resuscitation may potentiate ARDS, as angiotensin II increases pulmonary vascular permeability and worsens damage to the lung parenchyma¹⁴. Furthermore, angiotensin II stimulates aldosterone secretion, raising the risk of hypokalemia, which may necessitate more potassium supplementation to continue intravenous insulin to suppress ketogenesis⁵.

Recently, Coate et al.¹⁵ addressed the fundamental question of whether SARS-CoV-2 cell entry machinery is present in beta cells of human pancreatic tissue. By examining pancreatic ACE2 and transmembrane serine protease 2 (TMPRSS2) expression in normal donors and in those with diabetes, they found that (1) neither protein is detectable in alpha or beta cells; (2) ACE2 is primarily expressed in the islet and exocrine tissue capillaries, and a subset of ductal cells whereas TMPRSS2 is primarily expressed in ductal cells; (3) ACE2 and TMPRSS2 protein expression and distribution appear similar in normal donors and T2DM pancreas; and (4) ACE2 and TMPRSS2 are infrequently co-expressed in pancreatic ducts. Together, these mRNA and protein data do not support the hypothesis that SARS-CoV-2 can bind and infect islet alpha or beta cells and lead to cytotoxicity, causing their demise and eliciting new-onset diabetes. These results indicate that the impact of SARS-CoV-2 on glucose homeostasis is likely mediated by systemic inflammation or changes in organs such as liver, muscle, or adipose tissue.

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if inadequately treated. The onset and duration of cytokine storm vary, depending on the cause. Nearly all patients with cytokine storm are febrile, and the fever may be high grade in severe cases. The laboratory findings in cytokine storm are variable and influenced by the underlying cause. Non-specific markers of inflammation such as C-reactive protein are universally elevated and correlate with severity. Many patients have various blood-count abnormalities, such as leukocytosis, leukopenia, anemia, thrombocytopenia, and elevated ferritin and D-dimer levels. Prominent elevations in serum inflammatory cytokine levels, such as interferon- γ (IFN γ), interleukin-6 (IL-6), interleukin-10, and soluble interleukin-2 receptor alpha, a marker of T-cell activation, are usually present. Cytokine storm is not a diagnosis of exclusion, and it can encompass many disorders. Given the lack of a unifying definition for cytokine storm and disagreement about the distinction between cytokine storm and a physiologic inflammatory response, we proposed the following three criteria for identifying cytokine storm: elevated circulating cytokine levels, acute systemic inflammatory symptoms, and either secondary organ dysfunction (often renal, hepatic, or pulmonary) due to inflammation beyond that which could be attributed to a normal response to a pathogen (if a pathogen is present), or any cytokine-driven organ dysfunction (if no pathogen is present)¹⁶.

Although the mechanisms of lung injury and multiorgan failure in COVID-19 are still under investigation, reports of hemophagocytosis and elevated cytokine levels in affected patients, particularly those who are the most severely ill, suggest that cytokine storm may contribute to the pathogenesis of COVID-19. Serum cytokine levels that are elevated in patients with COVID-19 associated cytokine storm include interleukin-1b, IL-6, interferon-inducible protein 10, tumor necrosis factor, IFN γ , macrophage inflammatory protein 1a and 1b, and vascular endothelial growth factor¹⁷.

Compared with patients without diabetes, individuals with diabetes showed higher elevations in the

concentrations of IL-6, ferritin, C-reactive protein, and D-dimer foreshadowing a raging cytokine storm and a hypercoagulable state with rapid deterioration. The rapidly evolving renal failure, hypotension, pressor and steroid use, and variable nutritional support further complicates their management¹⁸.

In human monocytes, elevated glucose levels directly increase SARS-CoV-2 replication and glycolysis sustains SARS-CoV-2 replication through the production of mitochondrial reactive oxygen species (ROS) and activation of hypoxia-inducible factor 1 α . Therefore, hyperglycemia might support viral proliferation¹⁹.

Of note, glycemic deterioration is a typical complication of COVID-19 in patients with impaired glucose regulation or diabetes mellitus. In patients requiring insulin, SARS-CoV infection was associated with a rapidly increasing need for high doses of insulin (often approaching or exceeding 100 IU per day)²⁰.

SARS-CoV-2 leads to increased levels of inflammatory mediators in the blood, including lipopolysaccharide, inflammatory cytokines, and toxic metabolites. Modulation of natural killer cell activity (increased or decreased) and IFN γ production increase the interstitial and/or vascular permeability for pro-inflammatory products. In addition, infection with SARS-CoV-2 leads to increased ROS production. These effects lead to lung fibrosis, acute lung damage, and ARDS. ROS production and viral activation of the RAAS (through increased angiotensin II expression) cause insulin resistance, hyperglycemia, and vascular endothelial damage, all of which contribute to cardiovascular events, thromboembolism, and disseminated intravascular coagulation (DIC). Infection also causes increases in the clotting components fibrinogen and D-dimer leading to increases in blood viscosity and vascular endothelial damage, and associated cardiovascular events, thromboembolism, and DIC¹⁹.

Also known as CD26, dipeptidyl peptidase 4 (DPP4) is well recognized to have an important function in glucose homeostasis. In addition, DPP4 has an integral role in the immune system as a marker of activated T lymphocytes and a regulator of the expression of many chemokines, including CCL5, CXCL12, CXCL2 (also known as GRO-b) and CXCL11 (also

Table 1. Clinical characteristics of patients presenting with diabetic ketoacidosis

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age- yr	61	53	55	40	55
Sex	Male	Male	Male	Male	Male
Schooling- yr	3	12	9	6	9
Body mass index – kg/m ²	25	33.1	38.2	26	29.7
Medical history	Diabetes, former alcohol user	Diabetes	Diabetes, former alcohol user	Diabetes	Diabetes, undiagnosed hypertension
Medications	Metformin (1700 mg daily), Glibenclamide (5 mg daily)	Insulin glargine (10 UI daily), metformin (1700 mg daily)	Metformin (1700 mg daily)	Metformin (1700 mg daily)	Metformin (1700 mg daily)
Time to presentation- days	3	3	4	7	7
Signs and symptoms of DKA	Polydipsia, dry mucous membranes, tachycardia, Kussmaul breathing, glucosuria	Polydipsia, nausea, dry mucous membranes, tachycardia, glucosuria	Polydipsia, dry mucous membranes, tachycardia, Kussmaul breathing, glucosuria	Polydipsia, dry mucous membranes, tachycardia, Kussmaul breathing, glucosuria	Polydipsia, dry mucous membranes, tachycardia, glucosuria
COVID-19 symptoms	Fever, dyspnea, cough, lethargy	Fever	Fever, cough, headache, lethargy, sore throat	Fever, dyspnea, sore throat	Fever, dyspnea, cough, headache, lethargy
Findings on chest X-ray	Bilateral ground-glass opacities with bilateral patchy shadowing	Bilateral ground-glass opacities with bilateral infiltrates	Bilateral ground-glass opacities with infiltrates	Bilateral ground-glass opacities	Bilateral ground-glass opacities
Treatment for DKA	Intravenous sodium chloride 0.9% solution, intravenous insulin infusion, ceftriaxone (2 g daily) and azithromycin (500 mg daily)	Intravenous sodium chloride 0.9% solution, intravenous insulin infusion, potassium replacement, ceftriaxone (2 g daily) and clarithromycin (1 g daily)	Intravenous Hartmann solution, intravenous insulin infusion, ceftriaxone (2 g daily) and azithromycin (500 mg daily)	Intravenous sodium chloride 0.9% solution, intravenous insulin infusion, potassium replacement, ceftriaxone (2 g daily) and clarithromycin (1 g daily)	Intravenous sodium chloride 0.9% solution, intravenous insulin infusion, potassium replacement, ceftriaxone (2 g daily) and clarithromycin (1 g daily)
Maximum insulin infusion rate	12 U/ hour	10 U/hour	9 U/hour	14 U/hour	11 U/hour
Maximum temperature on hospitalization-°C	40	40.8	39	39	38.9
Complications on hospitalization	Shock, AKI, ARDS	ARDS	ARDS	ARDS	ARDS
Outcome status	Intubated and sedated, death at Day 2	Intubated and sedated, death at Day 3	Intubated and sedated, death at Day 2	Intubated and sedated, death at Day 9	Intubated and sedated, death at Day 8
Scores at admission					
NEWS2	7	9	7	8	6
MuLBSTA	11	7	9	9	6
PORT-PSI	146	103	135	50	75

(Continued)

Table 1. Clinical characteristics of patients presenting with diabetic ketoacidosis (continued)

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
SMART-COP	6	6	5	5	3
SCAP	16	20	32	5	6
SOFA	3	2	6	2	2
APACHE-II	15	8	16	2	7
Pneumonia severity (ATS 2019)	Severe	Severe	Severe	Nonsevere	Nonsevere
Arterial blood gas					
pH	7.23	7.25	7.16	7.20	7.26
Bicarbonate (mmol/L)	10.5	13.9	6.1	10.8	13
PaO ₂ mmHg	35	42	57	63	38
PaCO ₂ mmHg	25	24	17	17	23
PaO ₂ /FiO ₂ mmHg	166	200	274	300	180
Lactate mmol/L	1.2	0.9	1	0.8	1.1
Laboratory tests					
White cell count- mm ³	22000	15600	16800	9800	6500
Neutrophil count- mm ³	21400	13800	15300	8500	5100
Monocyte count- mm ³	1200	800	800	500	500
Lymphocyte count- mm ³	300	1000	600	800	800
Platelet count, mm ³	277000	202000	206000	359000	400000
Hemoglobin – g/dL	16.9	16.4	15.9	14	15
Venous glucose- mg/dL	381	324	376	273	354
Sodium- mEq/L	132	135	136	131	132
Chloride- mEq/L	103	98	102	93	101
Potassium – mEq/L	5.8	4.1	5.3	4	4.9
Anion gap	18.5	23	27.9	27.2	18
Urine ketones – mg/dL	150	100	150	100	150
Creatinine – mg/dL	1.5	0.72	3.67	0.61	0.8
D-dimer, ng/mL	3400	3580	3580	1170	1160
Lactate dehydrogenase, U/L	424	1007	906	433	510
Alanine aminotransferase, U/L	25	35	23	27	34
Aspartate aminotransferase, U/L	54	25	10	35	43
Total bilirubin, mg/dL	0.5	0.6	1.2	1.2	0.7
C-reactive protein, mg/dL	34.5	13.9	31.8	53.1	13.49
Procalcitonin, ng/dL	6	0.2	0.5	0.5	0

Reference ranges: White cell count, 4,600 to 10,200/mm³; neutrophil count, 2,000 to 6,900/mm³; monocyte count, 0 to 900/mm³; lymphocyte count, 600 to 3,400/mm³; platelet count, 142,000 to 424,000/mm³; hemoglobin, 12.2 to 18.1 g/dL; venous glucose, 70 to 110 mg/dL; arterial blood pH, 7.35 to 7.45; arterial blood bicarbonate, 22 to 28 mmol/L; PaO₂, 83 to 108 mmHg; PaCO₂, 35 to 45 mmHg; PaO₂/FiO₂, 400 to 500 mmHg; sodium, 136 to 145 mEq/L; chloride, 95 to 110 mEq/L; potassium, 3.5 to 5.3 mEq/L; anion gap, 8 to 16; urine ketones, < 5 mg/dL; creatinine, 0.8 to 1.4 mg/dL; D-dimer, 0 to 400 ng/mL; lactate dehydrogenase, 100 to 170 U/L; alanine aminotransferase, 0 to 41 U/L; aspartate aminotransferase, 0 to 38 U/L; total bilirubin, 0.1 to 1 mg/dL; c-reactive protein, 0 to 0.7 mg/dL; procalcitonin, 0 to 5 ng/dL.

+Scores on the National Early Warning Score (NEWS) 2 range from 0 to 20, with higher numbers indicating continuous monitoring of vital signs, emergent assessment by a clinical/critical care and usually transfer to higher level of care.

+Scores on the MuLBSTA score range from 0 to 20, with higher numbers indicating more 90-day mortality from viral pneumonia.

+Scores on the Pneumonia Patient Outcomes Research Team/Pneumonia Severity Index (PORT/PSI) range from 0 to >130, with a number higher than 130 indicating more mortality from community-acquired pneumonia.

+Scores on the SMART-COP range from 0 to 11, with higher numbers indicating an increased risk for needing intensive respiratory or vasopressor support.

+Scores on the SCAP (Severe Community-Acquired Pneumonia) range from 0 to 59, with higher numbers indicating more severe community-acquired pneumonia, including inpatient mortality, septic shock, or need for mechanical ventilation.

+Scores on the SOFA (Sequential Organ Failure Assessment) range from 0 to 24, with higher numbers indicating more mortality.

+Scores on the APACHE (Acute Physiology and Chronic Health Evaluation) II range from 0 to 71, with higher numbers indicating more mortality.

+ We defined the degree of severity of COVID-19 (severe vs. nonsevere) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia.

known as I-TAC). DPP4 inhibitors (DPP4is) are commonly used to decrease blood levels of glucose and to treat T2DM. Based on reports of upper respiratory tract infections, concerns have been raised about an increased risk of viral infections with DPP4 inhibition; however, evidence from clinical trials on the association between the use of DPP4is and the risk of community-acquired pneumonia in patients with T2DM does not confirm an increased risk¹⁹.

Although ACE2 is recognized as the main receptor, DPP4 might also bind to SARS-CoV-2. Certain polymorphisms of the DPP4 protein found in people in Africa were associated with a reduced chance of Middle Eastern respiratory syndrome coronavirus (MERS-CoV) infection. However, plasma levels of DPP4 in patients with MERS-CoV were statistically significantly reduced, suggesting a protective role of DPP4. Whether DPP4is affects the function of DPP4 as a viral receptor is a matter of debate²¹.

Interactions between DPP4 and the RAAS (including ACE2) have not been studied in detail but seem possible. DPP4 and the RAAS are linked genetically and are associated with the risk of SARS-CoV-2 infection and possibly the severity of COVID-19, particularly in patients with diabetes mellitus. This link is supported by the findings that DPP4 expression was increased in blood T lymphocytes from patients with T2DM and was correlated with insulin resistance, and upregulation of DPP4 in diabetic animals led to dysregulation of immune responses. More specifically, the receptor-binding domain of DPP4 interacts with adenosine deaminase (ADA) in CD4+ and CD8+ human T cells. This finding indicates a possible modulation of the host's immune system by SARS-CoV-2 through binding to DPP4 and competing for the ADA recognition site¹⁹.

The expression of DPP4 in the spleen, lung, liver, kidney, and some immune cells seems to be altered in patients with T2DM. Furthermore, DPP4 is not just a cell membrane protein but is shed into the circulation as soluble DPP4. Whether soluble DPP4 might have a role as a virus receptor or is protective during SARS-CoV-2 infection is entirely unclear. In an *in vitro* study, treatment with the DPP4is sitagliptin, vildagliptin, or saxagliptin did not block the entry of coronaviruses into cells. More detailed studies are

needed to fully characterize the role of DPP4is in patients with COVID-19 and T2DM^{19,22}.

CONCLUSIONS

Literature about DKA precipitated by any coronavirus infection is limited. SARS-CoV-2 may aggravate pancreatic beta-cell dysfunction and precipitate DKA. In this cases series of male patients with T2DM, reluctance to present to the hospital, severe pneumonia, high C-reactive protein (29.35 ± 14.74 mg/dl), high white cell count ($14,140 \pm 5,444$ mm³), high D-dimer (2578 ± 1155 ng/ml), high lactate dehydrogenase (656 ± 249 U/L), and BMI >25 Kg/m² may have contributed to their poor outcomes. We suggest that DKA in people with diabetes and SARS-CoV-2 infection is a frequent and lethal complication of diabetes mellitus.

AUTHORS' CONTRIBUTIONS AND ACKNOWLEDGMENTS

JM Alanís-Naranjo wrote the initial draft of the paper. EF Hammeken-Larrondo contributed to the discussion. MG Silva-Arroyo helped with the review of radiological images. All authors played a significant role in editing this case series.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

REFERENCES

1. Alsadhan I, Alruwashid S, Alhamad M, Alajmi S, Alshehri S, Alfadhli E, et al. Diabetic ketoacidosis precipitated by coronavirus disease 2019 infection: case series. *Curr Ther Res Clin Exp.* 2020;93:100609.
2. Dhataria KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers.* 2020;6:40.
3. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab.* 2020 Oct;22(10):1935-1941. doi: 10.1111/dom.14057.
4. Kim NY, Ha E, Moon JS, Lee YH, Choi EY. Acute hyperglycemic crises with coronavirus disease-19: case reports. *Diabetes Metab J.* 2020;44:349-53.
5. Chee YJ, Ng SJ, Yeoh E. Diabetic ketoacidosis precipitated by covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract* 2020;164:108166.
6. Orioli L, Hermans MP, Thissen JP, Maiter D, Vandeleene B, Yombi JC. COVID-19 in diabetic patients: related risks and specifics of management. *Ann Endocrinol (Paris).* 2020;81:101-9.
7. Schneider DA, von Herrath MG. Potential viral pathogenic mechanism in human Type 1 diabetes. *Diabetologia.* 2014;57:2009-18.
8. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol.* 2004;203:622-30.
9. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Zhonghua Bing Li Xue Za Zhi.* 2020;49:411-7.
10. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.* 2010;47:193-9.
11. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* 2020;126:1456-74.
12. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia.* 1998;41:127-33.
13. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol.* 2020;16:297-8.
14. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J Am Heart Assoc.* 2020;9:e016219.
15. Coate KC, Cha J, Shrestha S, Wang W, Gonçalves LM, Almaca 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;32:1028-1040.e4.
16. Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med.* 2020 Dec 3;383(23):2255-2273. doi: 10.1056/NEJMr2026131.
17. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *Int J Infect Dis.* 2020;95:332-9.
18. Gianchandani R, Esfandiari NH, Ang L, Iyengar J, Knotts S, Choksi P, et al. Managing hyperglycemia in the COVID-19 inflammatory storm. *Diabetes.* 2020;69:2048-53.
19. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol.* 2020;17:1-20.
20. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: insulin requirements parallel illness severity in critically unwell patients. *Clin Endocrinol.* 2020;93:390-3.
21. Kleine-Weber H, Schroeder S, Krüger N, Prokscha A, Naim HY, Müller MA, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. *Emerg Microbes Infect.* 2020;9:155-68.
22. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013;495:251-4.