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Diabetes ketoacidosis as the initial stage of diabetes mellitus in patients with COVID-19

The development of ketoacidosis or hyperosmolar hyperglycemic state has a pathophysiological basis, evidenced by the relationship already identified between the renin-angiotensin-aldosterone system (RAAS) and SARS-Co-V2. In addition to being expressed in the lung, angiotensin-converting enzyme 2 (ACE2), it is also found in the pancreas[1].

We want to share our single-center observation of five patients with COVID-19 admitted for new-onset diabetic ketoacidosis (DKA), that is, with non-known history of diabetes mellitus (DM). It is well known that acute hyperglycemic crises are significantly related to morbidity and mortality in people with diabetes[2].

All patients were diagnosed with COVID-19 by RT-PCR technique and radiological findings. DKA was diagnosed according to the ADA 2021 criteria[3], with pH < 7.3, bicarbonate < 18 mEq/l, glucose > 250 mg/dl, anion gap > 10 mEq/l and ketonemia.

The mean age was 39 years (between 28 - 57 years); four patients were overweight or obese; three died during hospitalization. For risk staging, we used COVID GRAM that classified four patients at intermediate risk of progression to invasive mechanical ventilation, and ABC-GOALS (validated in the Mexican population), which ranked the same four patients with a high risk of admission to the intensive care unit. Demographic and clinical data of these five patients with DKA and COVID-19 are presented in Table 1.

TABLE 1.– *Demographic and clinical data of five patients with DKA and COVID-19*

	Case 1	Case 2	Case 3	Case 4	Case 5
Years	28	57	34	48	32
Sex	M	F	F	M	F
Comorbidities	None	Overweight	Obesity grade I	Obesity grade II	Obesity grade I
Body mass index	24.2	28.3	34.6	36.3	30.4
COVID-GRAM (Points)	79	126	139	122	99
ABC Goals	7 points	8 points	12 points	13 points	8 points
Oxygen therapy devices	Reservoir Mask	IMV	IMV	Reservoir Mask	Nasal cannula high flow
FIO_2	40%	100%	100%	60%	32%
CAD Severity	Moderate	Mild	Serious	Serious	Mild
Glucose mg	266	455	420	294	313
PH	7.22	7.21	7.1	6.88	7.28
HCO_3mEq/	13.5	16.1	11	10.9	15.6
Days hospitalization	6	27	2	7	16
Dimer D ng/ml	890	1917	1266	161	1228
Ferritin mg/l	850	1200	698	250	223
Procalcitonin ng/ml	0.01	1.16	3.61	1.14	0.06
Albumin g/dl	3.2	2.3	2.05	3.38	3.66
Lymphocytes (103 /mm^3	900	600	2800	600	500
HDL UI/L	246	226	804	226	186
Over infection	Bacterial Pneumonia	Bacterial Pneumonia	Bacterial Pneumonia	Bacterial Pneumonia	None and Right Pyelonephritis
RALE RX	4	6	8	8	2
Troponin I ng/ml	2	6.9	4	350	14.7
BNP pg/ml	10	10	10	400	28.2
CPK mcg/l	44	60	64	6283	81
HBA1C %	12.5%	13%	9.5%	14%	8.9%
Discharge	Improvement	Death	Death	Death	Improvement

A diabetogenic effect induced by the SARS CoV2 virus has been postulated. It consists of the expression of the ACE2 in the pancreas, which causes damage to the beta-pancreatic cell. The metabolic effects are added to these mechanisms, and that results from the pro-inflammatory state triggered by the viral infection, that is related to the production of IL-6 and other cytokines, the increase in the synthesis of counter-regulatory hormones such as glucagon, catecholamines, cortisol, and the increase in critical metabolic disorders in the development of hyperglycemia (glycogenolysis and gluconeogenesis).

In our case series, the mean age was 39 years. Young adults with beta-cell functionality and negative autoimmunity markers are considered part of the clinical spectrum of type 2 diabetes prone to ketosis, a subgroup increasingly identified and possibly the most common phenotype in patients with ketosis. In contrast, other studies have reported the diagnosis of ketoacidosis in overweight and obese patients over 50 years of age, with higher insulin requirements and longer time to resolution of ketosis[4].

All the patients developed acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation. The two patients who required FiO_2 less than 40% could go home. We hypothesized that, regardless of the severity of ketoacidosis, the seriousness of SARS-Co-V2 pneumonia could have a greater weight in the prognosis of these patients.

The mean number of days of hospitalization was 11.6 days; the most serious case died two days after admission. The most prolonged hospitalization was 27 days and ended in death. In the analysis of the laboratory studies, we documented a significant variability of biomarkers. The D-dimer range was between 160-1917 ng/ml and ferritin between 223-1200 ng/ml. Procalcitonin was positive on admission in 3 patients in whom nosocomial pneumonia was diagnosed.

The two patients in invasive mechanical ventilation (IMV) had serum albumin less than 2.5 g/dl; hypoalbuminemia is a poor prognosis in patients with ARDS due to SARS-Co-V2[5]. The most severe case was a patient who did not presented lymphopenia, and a lactic dehydrogenase (DHL) of 804 mg/dl, so the clinical behavior may not be as expected in all cases. Only one of them presented myocardial damage with an elevation of troponin and brain natriuretic peptide (BNP); its outcome was death. Myocardial injury in COVID 19 is found in 6-20%. Its presence increases mortality to more than 50%[6].

The HbA1C range was between 8.9-14.0%, representing a significant prior glycemic loss, as it has been reported in Hispanic patients; the most crucial difference was the main difference at the time of diagnosis[7]. It is important to notice that the delay in diagnosis and treatment worsens the prognosis in adults.

We acknowledge that hospitalized patients have independent risk factors for developing KDA, especially when starting to receive parenteral steroids. New-onset KDA is more common in those with BMI < 25 kg/m^2, HbA1C > 8.3%, and IL-6 levels > 50.9 pg/ml. As we described, obese and overweight patients are the ones who most frequently debut with DKA-COVID-19, so this association should be seriously considered, and studied in more detail.

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