



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents available at [ScienceDirect](https://www.sciencedirect.com)

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



International
Diabetes
Federation



Clinical characteristics and outcome in patients with combined diabetic ketoacidosis and hyperosmolar hyperglycemic state associated with COVID-19: A retrospective, hospital-based observational case series

Kok Hoe Chan^{a,*}, Divya Thimmareddygar^a, Amr Ramahi^a, Liana Atallah^a,
Nicholas G. Baranetsky^{a,b}, Jihad Slim^{a,c}

^a Department of Medical Education, Saint Michael's Medical Centre, New York Medical College, NJ, United States

^b Department of Medicine, Saint Michael's Medical Centre, New York Medical College, NJ, United States

^c Department of Infectious Disease, Saint Michael's Medical Centre, New York Medical College, NJ, United States

ARTICLE INFO

Article history:

Received 5 June 2020

Accepted 17 June 2020

Available online 25 June 2020

Keywords:

SARS-CoV-2

COVID-19

Diabetic ketoacidosis

Hyperosmolar hyperglycemic state

ABSTRACT

Aim: One of the risk factors for poor outcome with SARS-CoV-2 infection is diabetes mellitus; diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most serious complications of diabetes mellitus. We aimed to explore the clinical characteristics and outcomes of COVID-19 patients presenting with combined DKA/HHS to our institution.

Methods: A retrospective, hospital based observation case series was performed on patients with SARS-CoV-2 admitted to Intensive Care Unit between 3/20/2020 and 4/20/2020. Inclusion criteria were: (1) Blood Glucose >250 mg/dL; (2) Serum bicarbonate <18 mmol/L; (3) Anion Gap >10; (4) serum pH <7.3; (5) ketonemia or ketonuria; (6) effective/calculated plasma osmolality >304 mOsm/kg and (7) positive SARS-CoV-2 RT-PCR.

Results: We reported 6 patients who presented during this period with combined DKA/HHS. Their median age was 50 years, all males, three Hispanic, and three African American. Hispanic patients, had more severe acidosis, and multiple comorbidities, with a higher mortality. The striking feature was that combined DKA/HHS was the initial presentation for COVID-19 for most of the cases.

Discussion: Our observational retrospective case series shows that diabetic patients are at risk of developing combined DKA/ HHS associated with COVID-19 and a substantial mortality. To our knowledge, we are first to report the clinical characteristics and outcome in this group of patients.

© 2020 Elsevier B.V. All rights reserved.

* Corresponding author at: Saint Michael's Medical Center, Newark, NJ 07101, United States.

E-mail address: kchan2@primehealthcare.com (K.H. Chan).

<https://doi.org/10.1016/j.diabres.2020.108279>

0168-8227/© 2020 Elsevier B.V. All rights reserved.

1. Introduction

A novel enveloped RNA beta-coronavirus was discovered in December 2019 and was found to belong to the same family as severe acute respiratory syndrome coronavirus (SARS-CoV), hence was called SARS-CoV-2 [1]. It is responsible for the current global pandemic with escalating cases and fatalities worldwide with over three million cases reported as of May 5th, 2020 [2]. According to the Chinese Center for Disease Control and Prevention (CDC), only 5 percent developed critical disease with multiple organ failure [3].

To our knowledge, combined DKA and HHS has not been reported in association with COVID-19 as of May 2020, despite the fact that DM is a well-known predisposing factor leading to severe COVID-19 disease [4]. In this retrospective, hospital based cohort study, we are reporting 6 patients who were admitted to the intensive care unit (ICU) for combined DKA and HHS with positive SARS-CoV-2 that had no other predisposing causes.

2. Methodology

A retrospective analysis was done on patients admitted to our intensive care unit between March 20th and April 20th, 2020. Inclusion criteria were: 1) Blood Glucose > 250 mg/dL; 2) Serum bicarbonate \leq 18 mmol/L; 3) Anion Gap > 10; 4) pH < 7.3; 4) ketonemia or ketonuria; 5) effective/calculated plasma osmolality > 304 mOsm/kg. and 6) positive SARS-CoV-2 RT-PCR. The only exclusion criteria was hyperglycemia without features of DKA/HHS.

Case definition of hyperglycemic crises - combined DKA and HHS on admission was: fulfilling the criteria above with pH < 7.3, bicarbonate < 18 mmol/L, Anion Gap > 10 and ketonemia with serum osmolality > 304 mOsm/kg.

Demographic analysis was performed, and data was expressed as counts, percentages or median and interquartile range (IQR). Cases were presented including history, hospital course, and outcome. SARS-CoV-2 RT-PCR was positive for all cases with elevated inflammatory markers (Table 1). All cases were managed with DKA/HHS protocol with aggressive hydration, insulin drip and electrolytes repletion. A waiver of HIPAA privacy authorization have been obtained through the institutional review board.

3. Case presentation

Case 1: A 48-year-old male with past medical history of type 2 diabetes mellitus (T2DM) presented to the emergency department (ED) with abdominal pain, nausea, vomiting and confusion. The patient was alert and awake but not oriented to time, place and person. Initial vital signs showed temperature 98.5 °F, heart rate (HR) 130/min, respiratory rate (RR) 12/min, blood pressure (BP) 110/68 mmHg, and oxygen saturation 99% on room air. Physical exam was notable for dry mucous membranes and cool extremities. Basic metabolic panel (BMP) and arterial blood gas (ABG) indicated combined DKA and HHS (Table 1). Electrolytes were within normal limit. Complete blood counts (CBC) showed Hgb 16.3 g/uL (13.5–16.5 g/dL), white blood count (WBC) 18,000/uL (4000–11,000/

uL), with absolute neutrophil count (ANC) 15,600/uL (1700–7000/uL) and absolute lymphocyte count (ALC) 500/uL (900–2900/uL). Chest X-ray (CXR) was normal. Electrocardiogram (ECG) showed normal sinus rhythm. Computed tomography (CT) head was within normal limits. He was admitted to intensive care unit (ICU) and was started on DKA/HHS protocol, hydroxychloroquine and doxycycline along with therapeutic anticoagulation. He recovered and was discharged home.

Case 2: A 52-year-old male with past medical history of T2DM, hypertension and coronary artery disease, presented to the ED complaining of generalized weakness, polyuria and polydipsia of two days duration. He claimed compliance with his medications. He denied any nausea, vomiting, cough, shortness of breath, fever, or chest pain. Initial vital signs showed temperature 97.9 °F, HR 104/min, RR 17/min, BP 121/54 mmHg, and oxygen saturation 98% on room air. Physical examination was within normal limits. BMP and ABG indicated combined DKA and HHS (Table 1). Electrolyte panel showed Na 130 mmol/L (135–145 mmol/L) and K 7.2 mmol/L (3.5–4.5 mmol/L). CBC were within normal limits. Urine drug screen (UDS) was positive for cocaine. CXR showed diffuse patchy bilateral opacities (Fig. 1a). ECG showed normal sinus rhythm (HR 96/min). He was treated with DKA/HHS protocol, one dose of ivermectin and 5 days course of doxycycline and metronidazole. He recovered and was discharged home.

Case 3: A 19-year-old male with no past medical history presented to ED complaining of abdominal pain, increased thirst, nausea and multiple episodes of vomiting. He denied any respiratory symptoms. No history of smoking or illicit drug use. Initial vital signs showed temperature 99.1 °F, HR 135/min, RR 45/min, BP 86/50 mmHg, and oxygen saturation 92% on room air. Physical examination was within normal limits except for morbid obesity (BMI 58.9 kg/m²). He was intubated in the ED due to altered mental status. BMP and ABG indicated combined DKA and HHS (Table 1). Electrolyte panel showed Na 117 mmol/L, K 5.7 mmol/L, and creatinine 3.2 mmol/L. CBC was significant for WBC 14,400/uL with ALC 900/uL. CXR showed low lung volumes with bilateral infiltrates (Fig. 1b). ECG showed atrial tachycardia. He was treated with DKA/HHS protocol, vasopressor and meropenem as well as doxycycline initially. He also received COVID-19 convalescent plasma. His renal function progressively deteriorated, ultimately requiring Continuous Veno-Venous Hemodialysis (CVVHD). His clinical status worsened with increasing oxygen requirements and persistent atrial flutter unresponsive to maximal therapy. He developed multi-organ failure and expired after 13 days of mechanical ventilation.

Case 4: A 38-year-old male with past medical history of T2DM was found to be unresponsive at home, cold extremities, and self-measurement blood glucose at home of more than 600 mg/dL. Initial vital signs showed temperature 88.9 °F, HR 59/min, RR 20/min, BP 80/26 mmHg, and oxygen saturation 90% on room air. On examination, he was lethargic with BMP and ABG indicated combined of DKA and HHS (Table 1). Electrolyte panel showed Na 123 mmol/L, K 4.4 mmol/L, UDS and ethanol levels were negative. CBC showed Hgb 9.1 g/dL, WBC 5500/uL with ANC 3700/uL and ALC 1000/uL. CXR showed bilateral infra-hilar infiltrates (Fig. 1c). He was started on DKA protocol, active rewarming, ceftriaxone and

Table 1 – Demographic characteristic, inflammatory markers and outcome.

Cases	Age	Sex	Ethnicity	BMI	HbA1c	Admitting BG	pH	Bicarb	Anion gap	BHOB	Calculated serum osmolality	CRP	LDH	D-dimer	Ferritin	Outcome
1	48	M	AA	25.2	13.6	1130	7.2	9.1	33	>4.5	365	8.3	263	4120	909	Stable
2	52	M	AA	23.6	12.1	683	7.24	11	21	>4.5	318	11.2	691	1220	1650	Stable
3	19	M	AA	58.9	10.9	1112	7.1	8	32	>4.5	307	8.1	695	1234	1628	Expired
4	38	M	Hispanic	24.2	N/A	1070	6.77	<5	>29	>4.5	347	2.6	275	834	807	Expired
5	62	M	Hispanic	24.1	13.3	604	7	6	29	N/A	323	13.2	397	1060	6671	Expired
6	62	M	Hispanic	30.5	N/A	959	6.86	6.6	>29	>4.5	358	N/A	N/A	N/A	3400	Expired
Average	46.8			31.1	12.5	926.3	7.03	8.1	28.8		336.3	8.7	464.2	1693.6	2510.8	
Median	50			24.7	12.7	1014.5	7.05	8.0	30.5		335.0	8.3	397.0	1220	1639	

M (Male), BMI (Body Mass Index), HbA1c (Hemoglobin A1c, normal range 4–5.6%), BG (blood glucose, normal range 70–140 mg/dL), pH (normal range 7.34–7.44), Bicarb (Bicarbonate, normal range 20–31 mmol/L), CRP (C-reactive protein, normal range 0–0.8 mg/dL), LDH (lactate dehydrogenase, normal range 122–222 U/L), D-dimer (0–500 ng/mL), Ferritin (24–336 ng/mL), Anion gap (5–15 mmol/L), BHOB (beta-hydroxybutyrate, normal range 0.02–0.27 mmol/L), Serum osmolality (278–305 mOsm/kg), N/A (not available).

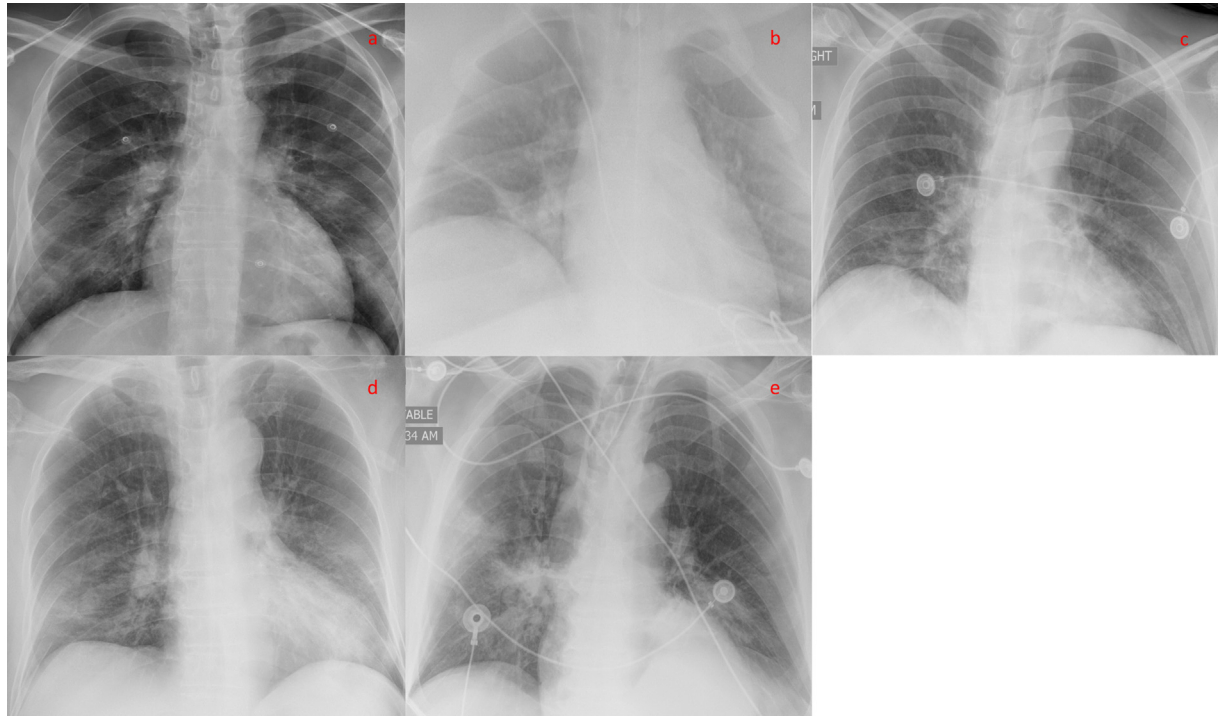


Fig. 1 – (a-e) Abnormal CXR on admission showing bilateral infiltrates consistent with COVID-19 disease.

doxycycline, and vasopressor. He was also intubated for airway protection. He ultimately expired with cardiopulmonary arrest.

Case 5: A 62-year-old male patient with past medical history of T2DM presented to the ED complaining of cough and shortness of breath. On initial encounter, he was alert and awake but disoriented. Initial vital signs were significant for BP 156/83 mmHg, HR 120/min, RR 33/min, and oxygen saturation 95% on room air. Initial physical exam was remarkable for reduced breath sounds all over the lung fields. BMP and ABG indicated combined DKA and HHS (Table 1). Electrolytes were within normal limits. UDS was negative. CBC showed WBC 15,100/uL, with ANC 13,100/uL and ALC 1300/uL. ECG showed sinus tachycardia and CXR showed diffuse bilateral patchy opacities (Fig. 1d). Blood cultures were negative. The patient was admitted to ICU and was started on DKA/HHS protocol, ceftriaxone and doxycycline. His DKA resolved but his respiratory status worsened in the ICU and he required mechanical ventilation. Unfortunately, he expired after three days.

Case 6: A 62-year-old male with past medical history of T2DM, hypertension, coronary artery disease and heart failure was brought to the ED by an ambulance after he was found to be unresponsive for an unknown duration. He had a cardiac arrest on his way to the hospital, basic life support was performed for a short period of time. Upon arrival to the ED, he was bradycardic with heart rate 30–35/min, which was treated with atropine and intubated. His initial vital signs showed temperature 91.1 F, BP was 77/40 mmHg with HR 130/min and RR 33/min. He had sluggish pupillary reflexes, absent gag and corneal reflexes and was not responding to painful stimulus. BMP and ABG indicated combined DKA and HHS (Table 1). Electrolyte panel showed Na 142 mmol/L and K

5.7 mmol/L. Cardiac enzymes and ethanol level were negative. Lactic acid 7.6 mmol/L, WBC 15,000/uL and ALC 1200/uL. CXR showed diffuse bilateral lung opacities (Fig. 1e). Blood and urine cultures were negative. He was started on DKA/HHS protocol, vasopressor, active rewarming, and ceftriaxone and doxycycline. However, a few hours later he became bradycardic with persistent hypotension and expired.

4. Result

Between March 20th to April 20th, 2020, 6 patients were admitted to our intensive care unit with diabetic crisis associated with COVID-19. BMP and ABG on all the patients were consistent with combined DKA and HHS. All patients had laboratory values fulfilling DKA/HHS defining parameters as tabulated in Table 1. The median age for the patient was 50 years old (range from 19 to 62 years old). All patients are male. Of the 6 patients, 5 patients (83%) had a history of DM, one patient was newly diagnosed DM, presenting as DKA/HHS, presumably precipitated by COVID-19. Only 2 patients (33%) had a BMI \geq 30 kg/m². As for ethnicity; three were Hispanic (50%), and three African American (50%).

The average hemoglobin A1c was 12.5% (ranged from 10.9 to 13.6%, no data for two patients). The average admitting plasma glucose was 926.3 mg/dL (ranged from 604 to 1130 mg/dL). The average serum osmolality was 336.3 mOsm/kg (ranged from 307 to 358 mOsm/kg). Though statistical analysis could not be done due to small number size, patients with Hispanic ethnicity, severe acidosis with multiple comorbidities tended to have higher mortality. Four of six (67%) of the patients expired. Nonetheless, the extent of inflammatory markers elevation does not seem to correlate with the mortality. Those who required mechanical ventila-

tion had a worse prognosis. There were four patients who required mechanical ventilation, and all expired. Another notable finding from this case series is that, the majority of patients presented with DKA/HHS symptoms rather than respiratory symptoms, and SARS-CoV-2 was detected mainly because our institution in the epicentre of the pandemic and all admissions were screened for COVID-19.

5. Discussion

Infection is a well-documented precipitating factor for combined DKA and HHS in both new-onset and established diabetes. Patients with long-standing diabetes frequently have other co-morbidities including hypertension, cardiovascular disease, obesity, and chronic kidney disease. All of which have been established as risk factors for severe COVID-19 [4,5]. A retrospective analysis conducted in China observed an increased risk of mortality in diabetic patients with COVID-19 infection. Better glucose control has been associated with improved outcomes in this group of patients as compared to those with poorly glucose control [4].

The mechanism of how SARS-CoV-2 could precipitate DKA is poorly understood. SARS-CoV-2 belong to the family of SARS coronavirus which has been shown to affect both exocrine and endocrine cells of pancreas [6]. Diabetes has been associated with poor outcomes in prior coronavirus epidemics like SARS-CoV [7] and Middle East Respiratory Syndrome (MERS) Coronavirus [8]. It has been postulated that diabetes predisposes to dysregulated immune response (with elevated Interleukin-17 α) resulting in lung pathology [9].

It has been established that Angiotensin-Converting Enzyme 2 (ACE2) serves as a functional receptor for SARS-CoV-2 S-protein, similar to SARS-CoV [10]. ACE2 is known to be expressed in lungs, heart, kidneys, gastrointestinal system, and pancreas [10]. ACE2 receptors are also found in the exocrine and islet cells of the pancreas [11]. The canine pancreas was shown to have local angiotensin peptide generating system, with Angiotensin II predominant [12]. ACE2 typically degrades Angiotensin II to Angiotensin (1–7), one of the active heptapeptides in the renin angiotensin system. Angiotensin II can delay insulin secretion and decrease blood flow to islet-cells resulting in hyperglycemia, local inflammation, apoptosis and decreased proliferation of islet cells [13]. Angiotensin (1–7) counteracts this effect by increasing insulin secretion and vasodilatation. SARS-CoV-2 binding to ACE2 may result in downregulation of ACE2, leading to an unopposed action of Angiotensin II. SARS-CoV-2 could also have a direct effect on islet-cells, leading to acute islet-cell dysfunction, decreased insulin release and subsequent acute hyperglycemic crisis and even ketosis [11]. Nonetheless, there is still lack of data on the mechanism of SARS-CoV-2 effect on the pancreatic angiotensin system and islet-cells.

Studies have shown that patients with diabetes are at risk for severe COVID-19 [4]. In our patients, there was 67% mortality and 67% required mechanical ventilation. All ventilated patients ultimately expired. Hispanics, severe acidosis and multiple comorbidities tended to be associated with higher mortality, which is consistent with retrospective cohort analysis reported in China and United States [3,4,14,15]. Age in

particular, in our case series, did not appear to influence the mortality, however, the sample size is relatively small. Pasqual et al. reported that combined DKA and HHS has higher mortality as compared to isolated DKA and HHS alone [16]. In this hospital based retrospective study, we observed the same trend with 67% mortality in patients with combined DKA and HHS.

Managing DKA with or without HHS associated with COVID-19 poses a great challenge. Currently, there is no consensus guideline on how to manage this group of patients. Fluid management is a particular concern, in addition to maintaining adequate hydration to prevent acute renal failure, there is also a need to maintain negative fluid balance to prevent patient progressing into Acute Respiratory Distress Syndrome (ARDS), which is a major complication in patients with COVID-19. All our patients were managed with fluids hydration, insulin drip and electrolytes replacement. In addition, bicarbonate was given if the pH was ≤ 6.9 . Kidney function and electrolytes were monitored to ensure adequate hydration while at the same time trying to prevent volume overload.

To our knowledge, this is the first retrospective, observational case series summarizing the clinical characteristics and outcome of combined DKA and HHS patients associated with COVID-19. A comprehensive cohort study is paramount to explore the degree of blood sugar control and its impact on the severity of infection in COVID-19 patients. In addition, more studies are needed to dissect the interplay between SARS-CoV-2 and pancreatic angiotensin system, in order for us to have a better understanding on the pathogenesis of SARS-CoV-2 induced hyperglycemia, and combined DKA and HHS.

6. Conclusion

Our observational retrospective case series shows that diabetic patients are at risk of developing combined DKA and HHS associated with COVID-19. Hispanic, poor blood glucose control, mechanical ventilation and severe acidosis seems to be the poor prognostic features in this group of patients. It is paramount to have a tight glucose control in both inpatient and outpatient setting, when managing diabetic patients. Further studies are needed to established the degree of hyperglycemia as the predictors for mortality and morbidity in COVID-19 patients. Moreover, we need to understand the pathogenesis of SARS-CoV-2 on the pancreatic angiotensin system, so as to monitor the effect of SARS-CoV-2 on the pancreas in long term.

Funding

The authors received no funding from an external source.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

- [1] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020 Feb 22;395(10224):565–74. doi: 10.1016/S0140-6736(20)30251-8. Epub 2020 Jan 30. PMID: 32007145; PMCID: PMC7159086.
- [2] WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020 [Internet]. World Health Organization. World Health Organization; [cited 2020Apr28]. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>.
- [3] CDC COVID-19 Response Team. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019—United States, February 12–March 28, 2020. *MMWR Morb Mortal Wkly Rep*; 2020.
- [4] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- [5] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 2020. <https://doi.org/10.1001/jama.2020.2648>.
- [6] Shi X, Gong E, Gao D, et al. Severe acute respiratory syndrome associated coronavirus is detected in intestinal tissues of fatal cases. *Am J Gastroenterol* 2005;100(1):169–76. <https://doi.org/10.1111/j.1572-0241.2005.40377.x>.
- [7] Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006;23(6):623–8. <https://doi.org/10.1111/j.1464-5491.2006.01861.x>.
- [8] Alqahtani FY, Aleanizy FS, Ali El Hadi Mohamed R, et al. Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study [published online ahead of print, 2018 Nov 5]. *Epidemiol Infect*. 2018;147:1-5. doi: 10.1017/S0950268818002923.
- [9] Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI Insight* 2019;4(20):e131774. Published 2019 Oct 17. doi: 10.1172/jci.insight.131774.
- [10] Hofmann H, Pyrc K, van der Hoek L, et al. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc Natl Acad Sci USA* 2005;102:7988.
- [11] 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. <https://doi.org/10.1007/s00592-009-0109-4>.
- [12] Chappell MC, Millsted A, Diz DI, Brosnihan KB, Ferrario CM. Evidence for an intrinsic angiotensin system in the canine pancreas. *J Hypertens* 1991;9(8):751–9. <https://doi.org/10.1097/00004872-199108000-00008>.
- [13] 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(2):127–33. <https://doi.org/10.1007/s001250050880>.
- [14] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335.
- [15] Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. *Clin Infect Dis* 2020.
- [16] Pasquel FJ, Tsegka K, Wang H, et al. Clinical outcomes in patients with isolated or combined diabetic ketoacidosis and hyperosmolar hyperglycemic state: a retrospective, hospital-based cohort study. *Diabetes Care* 2020;43(2):349–57. <https://doi.org/10.2337/dc19-1168>.