NEW ONSET DIABETES AND DIABETIC KETOACIDOSIS IN COVID-19 PATIENTS: CASE REPORT AND REVIEW OF LITERATURE

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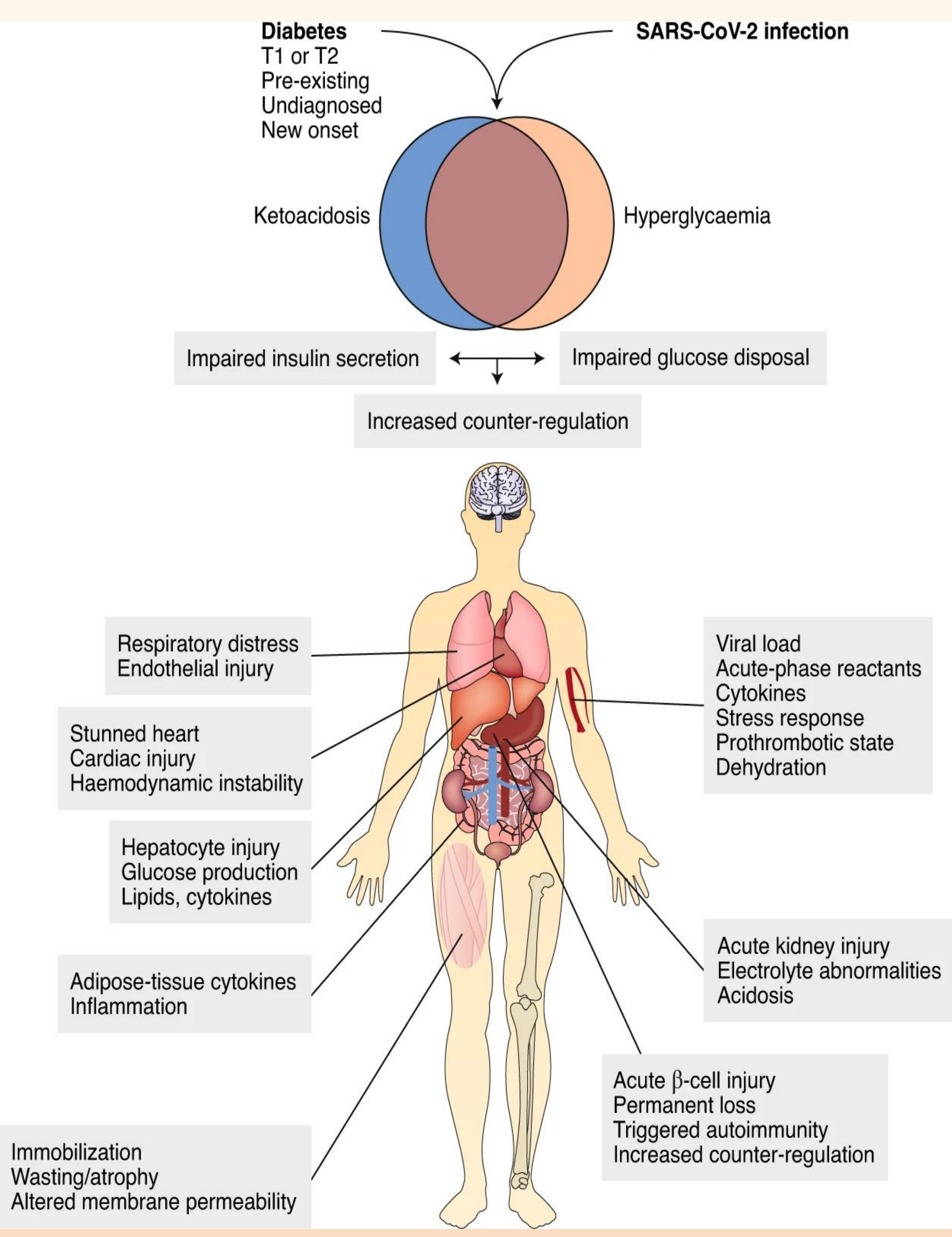
INTRODUCTION

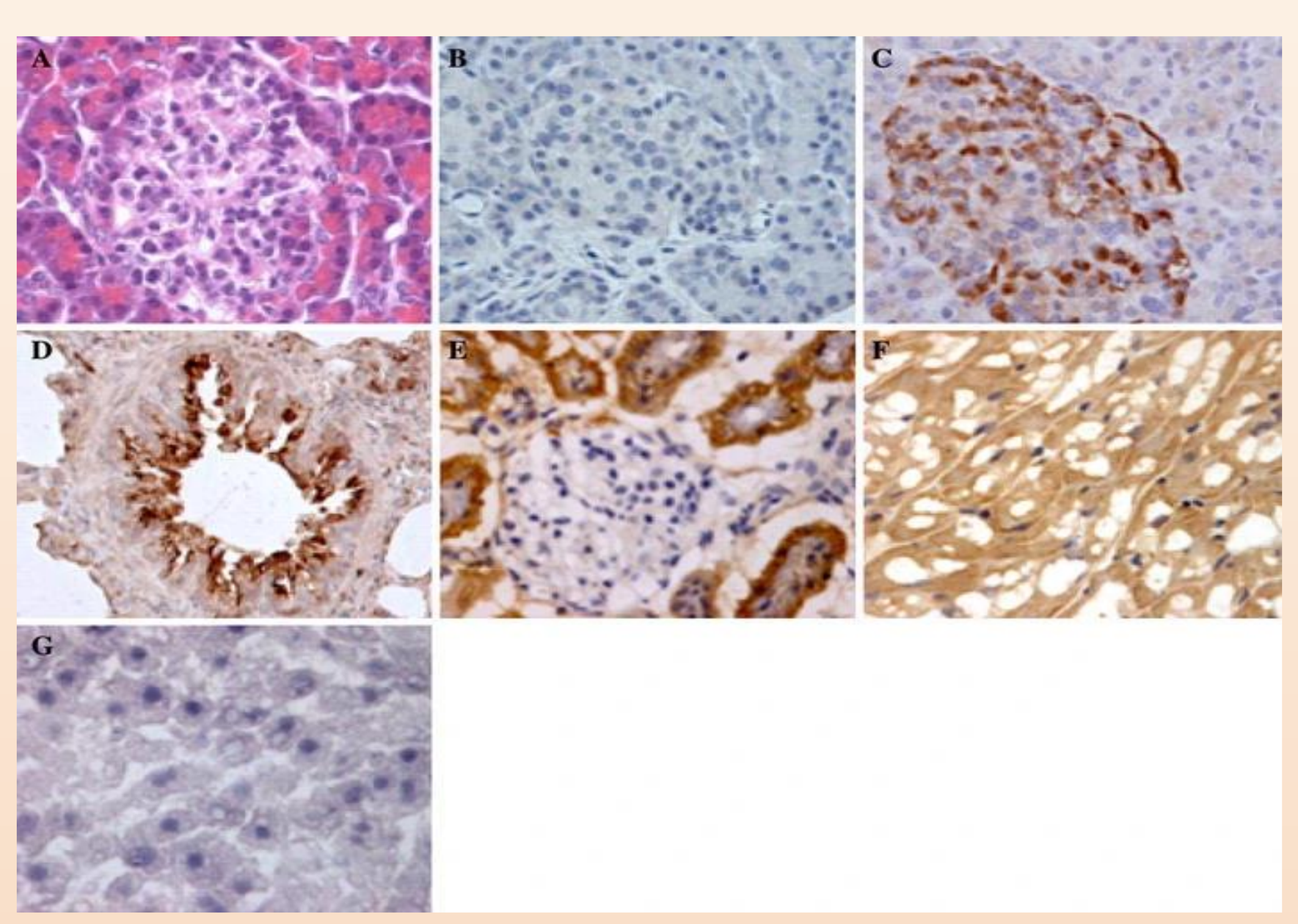
- The clinical presentation of COVID-19 infection ranges from dyspnea, cough, fever, myalgias to anosmia and diarrhea. Severity spectrum of this disease varies from asymptomatic presentation to sudden death[1,2]. Diabetes in these patients can lead to worse outcome[3,4].
- COVID-19 infection is known to cause hyperglycemia in diabetics and exacerbate complications[5]. However, there have been very few reported cases of COVID-19 infection presenting as diabetic ketoacidosis (DKA) and henceforth, precipitating a new diagnosis of diabetes mellitus[6].
- Our review of literature for new-onset diabetes in COVID-19 included 6 previous case studies; only one had 63.6% mortality. There were 2 retrospective studies as well with mortality rate of 38.5% and 14%. Further research is needed to evaluate if there is a casualty relationship between COVID-19 infection and the development of DKA and new-onset diabetes.
- However, there have been very few reported cases of COVID-19 infection presenting as diabetic ketoacidosis (DKA) and henceforth, precipitating a new diagnosis of diabetes mellitus.



The findings of hyperglycemia and ketoacidosis in patients with COVID-19 have prompted the question of whether there is underlying diabetes, regardless of whether it was previously recognized. Ketoacidosis can occur independently of hyperglycemia even in patients who are not being treated with sodium/glucose cotransporter Sglt2 inhibitors. The mechanisms of these metabolic abnormalities involve impaired glucose utilization as well as decreased insulin secretion or increased counter-regulation. Examples of salient pathophysiologic features at the intersection of diabetes, acute intercurrent illness of any kind and COVID-19-specific factors are shown next to each target organ. Depending on the clinical course, these abnormalities may unfold in a rolling fashion rather than all at once. Source: Accili, D. Can COVID-19 cause diabetes?. *Nat Metab* **3,** 123–125 (2021). https://doi.org/10.1038/s42255-020-00339-7

METHODS

- We report a case without prior history of diabetes presenting with altered mental status (AMS) associated with DKA as the initial presentation of COVID-19 infection, and the current literature was reviewed.
- A 62-year-old female with history of hypertension presented to emergency room with chief complaint of AMS and slurred speech since 24 hrs. associated with cough, myalgias, and decreased appetite for 3 days.
- She had received three doses of COVID vaccine, including booster dose one month back. Her vital signs showed blood pressure of 125/83 mm/Hg, heart rate of 119 beats per minute, Temperature at 97 °F orally, Respirations at 30 breaths per minute, SpO2 at 78% on room air and BMI of 33.11 kg/m2.
- Upon presentation, she was alert, oriented x1, without any sensory or focal deficits. Laboratory investigations showed hyperglycemia (blood glucose of 599 mg/dL), high anion gap metabolic acidosis (anion gap of 29.3, pH 7.13, HCO3 was 6.3 mmol/L) and ketonemia (beta-hydroxybutyrate of 8.48 mmol/L), confirming the diagnosis of DKA. She also had leukocytosis, hypernatremia and raised inflammatory markers. Her COVID-19 PCR-testing was positive. Her chest x-ray showed bilateral reticulonodular infiltrates while computed tomography of head and urine drug screen were negative.
- She was admitted to ICU and received 6L of intravenous fluids and intravenous insulin infusion in the first 24hrs.

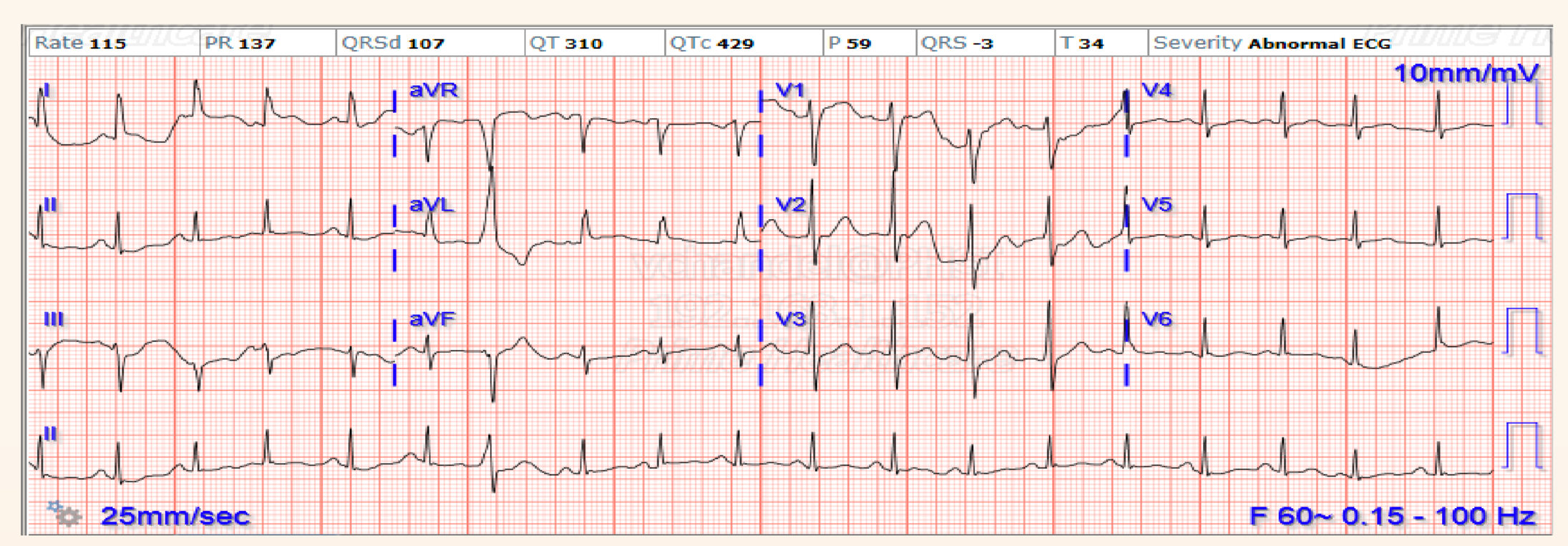


Immunohistochemically specific pattern of staining for SARS-CoV-2 receptor protein in different organs. Serial sections of the pancreas. **a** Hematoxylin-eosin (HE) stain shows the exocrine tissue of pancreas (*red*) with a pancreatic islet (in the *middle*). **b** Negative immunostaining control shows no non-specific staining especially caused by endogenous biotin. **c** Expression of ACE2 in pancreas as assessed by immunohistochemistry shows endocrine tissue is strongly positive compared with exocrine tissue. **d** Lung: marked ACE2 immunostaining was found in type I and type II alveolar epithelial cells, and capillary endothelium. **e** Kidney: ACE2 was very weakly present in glomerular visceral and parietal epithelium, but strongly present in the brush border and cytoplasm of proximal tubular cells, and in the cytoplasm of distal tubules and collecting ducts. **f** Heart: ACE2 was present in the myocytes, myocardium, border zone, endothelium of small-to-large arteries as well as sporadically within the smooth muscle of these vessels. **g** Liver: Küpffer cells, hepatocytes, and the endothelium of sinusoids were negative. Source: Yang, JK., Lin, SS., Ji, XJ. et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 47, 193–199 (2010). https://doi.org/10.1007/s00592-009-0109-4.

LITERATURE REVIEW AND IMAGES

	Reference	Study type	Country of origin	Population	Comorbidities	Family History	Presenting Symptoms	Diagnosis of Diabetes mellitus	Timing & Diagnosis of COVID-19	Management of DM/DKA	Management of COVID-19	Outcome
1	Suwanwongse et al. 2021	Case Series	USA	n=1, 18 y/o M	Obesity	DM2	Fatigue, polydipsia, and polyuria	Hyperglycemia, high anion gap metabolic acidosis, and ketonemia. Urine analysis showed a large amount of sugar and ketone.	COVID-19 RT-PCR positive at time of admission	Insulin drip, intravenous hydration, replacement of electrolytes, and supportive measures.	No specific COVID-19 treatment was given	Discharged home with a subcutaneous insulin regimen and metformin on hospital day 3.
2		Case Series	USA	n=1, 6 51y/o M	Obesity	None	Fatigue, anorexia, polyuria, polydipsia, weight loss	Hyperglycemia, high anion-gap metabolic acidosis, and ketonemia	COVID-19+ two month prior. Repeat SARS-CoV-2 RT-PCR at time of admission was negative.	Subcutaneous insulin, aggressive intravenous hydration, electrolytes replacement and supportive measures	No specific COVID-19 treatment was given	Discharged with a subcutaneous insulin regimen on day 3.
3		Case Series	USA	n=1, 64 y/o F	Breast cancer in remission	DM	Polyuria and polydipsia	Hyperglycemia. Urine analysis showed a large amount of sugar and a small amount of ketone.	Tested positive for COVID-19 ten weeks prior	Intravenous fluid	No specific COVID-19 treatment was given	Discharged home on oral metformin
4	Pavan Kumar Reddy et al.	Case Series	India	n=1, 30 y/o M	None	None	Weakness, fever, loss of taste and mild dyspnea.	Plasma glucose of 555 mg/dL , metabolic acidosis, urine ketones were present. HbA1c was 9.6%.	Xray chest: patchy airspace opacities in bilateral lung fields and CT chest: ground-glass opacities in bilateral upper lobes consistent with moderately severe COVID-19	Intravenous fluid replacement followed by intravenous insulin infusion.	Remdesivir, empirical antibiotics, steroids	Discharged home.
5		Case Series	India	n=1, 60 y/o M	Hypertension, Stroke	None	Sudden onset uneasiness and inability to move the left upper limb associated with weakness of left lower limb.	Random blood glucose was 582 mg/dL and HbA1c was 12.6%. Urine ketones present.	COVID-19 RT-PCR +	Intravenous fluid, intravenous insulin infusion with monitoring of serum electrolytes.	Remdesivir, empirical antibiotics.	Discharged home.
6	Ashley I. Heaney et al.	Case Report	USA	n=1, 54 y/o M	Hypertension, kidney stones, testicular hypofunction and erectile dysfunction	NR	Shortness of breath	Hyperglycemia, anion gap metabolic acidosis and ketonuria, blood glucose of 463 mg/dL	Tested positive one week prior in outpatient. Rapid COVID-19 at time of admission was positive.	2 L of normal saline, insulin drip, electrolytes monitoring.	No specific COVID-19 treatment was given	Discharged to home on hospital day 5
7	Ying Jie Chee et al.	Case Report	Singapore	n=1, 37 y/o M	None	NR	Fever, vomiting, polydipsia and polyuria	Laboratory investigations were significant for hyperglycemia, high anion gap metabolic acidosis and ketonemia, confirming the diagnosis of DKA.	Positive contact history	6 L of intravenous fluids and intravenous insulin infusion in the first 24 h. Serum electrolytes monitoring.	No specific COVID-19 treatment was given	DKA resolved on 2nd day of admission
8	Balraj Singh, MD et al.	Case Series	USA	n=11, 7 male and 4 female, median age was 47 years (range 12-88 years).	Hypertension, dyslipidemia, asthma, anxiety, depression, coronary artery disease, and gout.	NR	Altered mental status, weakness, SOB, cough, fever, vomiting, abdominal pain, chest pain, and foot pain.	Median value of glucose on presentation was 974 mg/dL (range 549-1556 mg/dL), and hemoglobin A1c was 13.8%. The median value of anion gap was 34 mEq/L. Out of the 11 patients, ketonemia was moderate in 6 patients, large in 3, and small in 2 patients.	Out of 11 patients, pneumonia was diagnosed at presentation in 8 patients, while in 3 patients, chest X-ray was clear.	All patients received standard treatment protocol for combined DKA and HHNK with intravenous insulin infusion and intravenous fluids.	Out of the 11 patients, 6 required mechanical ventilation	Out of 11 total patients, 7 patients died. All the 6 patients requiring mechanical ventilation died.
9	Smith et al, 2021	Retrospective study, spanning over 7 wk	USA	n = 184, M/F = 98/86. Avg age = 64.4 yr (21-100)	hypertension (60.3%), hyperlipidemia (33.7%), dementia (13.0%), chronic kidney disease (13.0%), coronary artery disease (12.0%), and congestive heart failure (10.9%)	NR	hypoxia (83.7%) and fever (62.5%)	A new diagnosis of DM was made in patients previously unaware of their condition based on an HbA1C > 6.4%.	COVID-19 diagnosis based on: 177 patients: Confirmed positive lab test for SARS-CoV-2. Remaining (7 patients): Clinical diagnosis.	diabetes status was also associated with increasing rates of intubation. Among 25 patients with no diabetes and normal HbA1C levels, only one (4.0%) required intubation. Of patients with preDM, 18.5% (10 of 54) were intubated, while 28.85% (30 of 104) of patients with DM required intubation.	Among 184 hospitalized patients receiving full care for COVID-19, 44 (23.9%) required intubation.	DM = 114/184 (New-onset DM= 29/184). 111 patients lived and were never intubated; 58 patients were intubated and/or expired; 44 patients expired
10	Fadini et al, 2020	Retrospective study	Italy	n (Total) = 413. Median observation time of 17 d	Cardiovascular disease, atrial fibrillation, CKD, COPD, cancer	NR	Fever, cough, pneumonia, dyspnea, GI symptoms	Newly-diagnosed diabetes: defined by HbA1c 48 mmol/mol (6.5%) or higher; in the absence of an HbA1c determination, a random glucose level of 11.1 mmol/l (200 mg/dl) or higher, accompanied by signs and symptoms of hyperglycemia was considered diagnostic. Newly-diagnosed diabetes = 21/413	Positive PCR test for SARS-CoV-2 on upper or lower airway sample	For each 2 mmol/l (36 mg/dl) higher admission glucose, the probability of severe progression of COVID-19 significantly increased by 15%. The association between hyperglycemia and COVID-19 severity was significantly stronger for patients with newly-diagnosed diabetes than for those with pre-existing diabetes.	Low-flow and high-flow oxygen, non-invasive ventilation, intubation, lopinavir/ritonavir, azithromycin, remdesivir, chloroquine/hydroxychloroquine, glucocorticoids, tocilizumab.	No diabetes = 306/413. Diabetes = 107/413 (Pre- existing diabetes = 86/413; Newly-diagnosed diabetes = 21/413). Primary Outcome (composite of ICU admission or death): 62/306 (20.3%); 7/86 (31.4%); 13/21 (61.9%). Death: 33/306 (10.8%); 12/86 (14.0%); 3/21 (14.3%). Discharged alive: 238/306 (77.8%); 51/86 (59.3%); 9/21 (42.9%).
11	Marchand et al, 2020	Case Report	France	n=1, 29 y/o F	Obesity	DM	Polyuria–polydipsia syndrome	Glycemia of 3.7 g/l (20.5 mmol/l), non-significant ketosis (0.7 mmol/l), HbA1c level was 11.8%	SARS-CoV2 serology was positive at time of admission, confirming previous symptomatic COVID-19 infection two months prior	treated with basal bolus insulin regimen	No specific COVID-19 treatment was given	No information on severity or outcome of COVID-19
12	Our report	Case Report	USA	n=1, 62 y/o F	Hypertension, Hypothyroidism	None	Altered mental status, weakness, SOB, cough, fever, vomiting.	Hyperglycemia, high anion gap metabolic acidosis, and ketonemia	COVID-19 RT PCR+, Patient was vaccinated with 3 doses of Pfizer.	6 L of intravenous fluids and intravenous insulin infusion in the first 24 h. Serum electrolytes monitoring.	Remdesivir, Tocilizumab and Steroids	Discharged to rehabilitation on second week

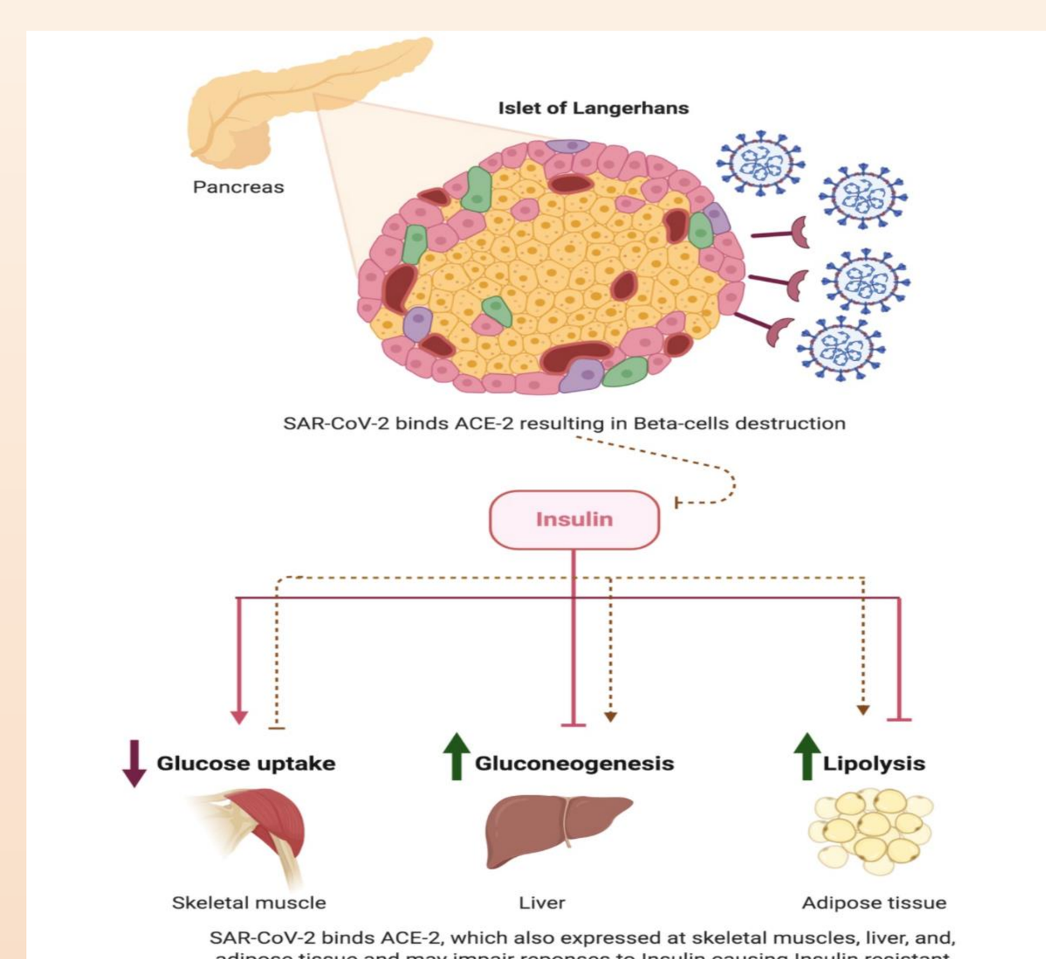
NR: Not reported, DM: Diabetes mellitus, SOB: Shortness of breath, RT-PCR: Reverse transcriptase Polymerase chain reaction, CT: Computed tomography, M: Male, F: Female.



Electrocardiogram showing sinus tachycardia, multiform premature ventricular complexes, abnormal R-wave progression (early transition) and borderline repolarization abnormality.

Laboratory parameters	Day of admission	Reference range
WBC (1000/mm³)	15.2	4.5-11
Absolute neutrophils (1000/mm³)	12.4	1.7-7.0
Hemoglobin (g/dL)	11.4	12.5-15.5
RBC (mi/mm³)	3.69	4.32-5.72
Platelets (1000/mm³)	550	150-450
Glucose (mg/dL)	599	70-140
Blood Urea Nitrogen(mg/dL)	52	6-24
Creatinine (mg/dL)	1.6	0.6-1.2
AST (U/L)	26	10-36
ALT (U/L)	31	9-46
Alkaline phosphatase (U/L)	166	40-115
Bilirubin (mg/dL)	0.6	0.2-1.2
Sodium (mg/dL)	151	136-145
Potassium (mmol/L)	4.0	3.5-5.3
Troponins (ng/ml)	<0.017	0.000-0.056
Lactate (mmol/L)	1.2	0.5-2.2
INR	1.18	0.8-1.2
Glycosylated hemoglobin (%)	12.2	4.0-5.6
pH	7.132	7.340-7.440
Bicarbonate (mmol/L)	6.3	22-28
pCo2 (mmHg)	19.2	35-45
pO2 (mmHg)	57.1	80-100
Beta Hydroxybutyrate (mmol/L)	8.48	0.4-0.5
Anion gap (mEq/L)	29.3	8-12
D-Dimer (g/dL)	4.67	<0.05
Lactate Dehydrogenase (U/L)	511	140-280
C-reactive protein (mg/L)	304.2	8-10
Ferritin (mcg/L)	6266	24-336

Laboratory parameters in our patient during his admission. WBC: White blood cells, RBC: Red blood cells, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio.



Pathophysiology of diabetes in COVID-19 infection: SARS-CoV-2 interaction with Angiotensin Converting Enzyme -2 leading to insulin resistance and henceforth, either new onset diabetes or expression of previously masked diabetes.

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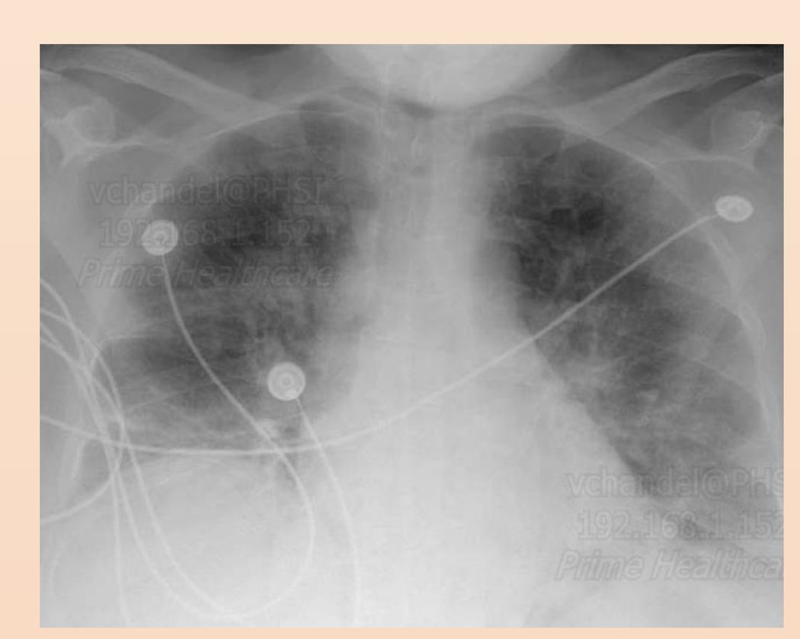
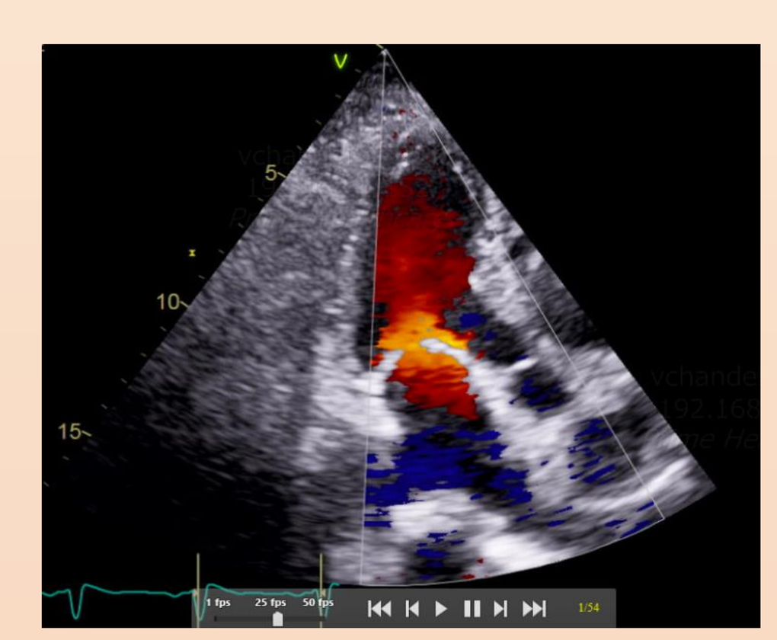


Initial Chest X-ray of our patient showing bilateral patchy pulmonary infiltrates consistent with COVID-19 infection.



Echocardiogram of our patient on presentation showing normal wall motion, normal diastolic function and left ventricular ejection fraction at 65-70%

RESULTS

- Patient had uneventful resolution of DKA 2-days after ICU admission. She also received steroids, remdesivir and tocilizumab. Once stable, she was discharged saturating >95% on room air.
- Deficiency of insulin and increased counter-regulatory responses leads to higher ketones precipitating DKA. The interactions between SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) can be a suggestive mechanism of DKA in our patient[7].
- Angiotensin-converting enzyme 2 (ACE2) which is highly expressed in lungs and pancreas, catalyzes the conversion of angiotensin II to angiotensin (1–7) and serves as the entry point for SARS-CoV-2. Henceforth, entry of SARS-CoV-2 into pancreatic islet cells can directly aggravate beta cell injury[8].
- ACE2 expression is downregulated after endocytosis of the virus complex[9] causing unopposed angiotensin II, which may impede insulin secretion[10]. These factors can lead to acute worsening of pancreatic beta-cell function, precipitating DKA in our patient[11].
- Other possible mechanism is that COVID-19 infection likely unmasked unknown and preexisting diabetes by aggravating its metabolic complications due to release of inflammatory cytokines[12] during this acute viral illness, rather than causing the new-onset diabetes mellitus.

CONCLUSIONS

- Following diagnosis of COVID-19 related hyperglycemia, patients should be kept on low threshold screen for development of new-onset diabetes or unmasking of a previously undiagnosed diabetes.

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