Diabetic ketoacidosis precipitated by COVID-19 in patient with newly diagnosed diabetes mellitus

Abstract. Background. Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diabetes mellitus (DM) have been reported frequently in patients with the new corona virus disease — 2019, COVID-19. It has been associated with progressive course and worse outcome. There is scarce data on diabetic ketoacidosis (DKA) in COVID-19 infection. There has been several cases reported on COVID-19 infection precipitating a new diagnosis of type 2 DM (T2DM). However, there is a lack of evidence regarding type 1 DM (T1DM). We report a case of DKA precipitated by COVID-19 in a patient with newly diagnosed T1DM. Recently, case reports and small cross-sectional studies described diabetic patients who develop DKA when infected with COVID-19. The incidence of DKA has been found to be high in patients with T1DM and T2DM admitted to hospital with COVID-19. Case presentation. We present a 29 year-old, previously healthy man with 5 days history of fever, fatigue, vomiting, polydipsia and polyuria. His lab results showed high blood glucose, high anion gap metabolic acidosis and ketonuria diagnostic of DKA. He also tested positive for COVID-19 and his Chest CT was consistent with bilateral COVID 19 pneumonia (ground-glass opacity, consolidation, and crazy-paving pattern). He was successfully managed with intravenous fluids and insulin as per DKA protocol. He required intravenous antibiotics, steroids and oxygenotherapy for COVID-19 pneumonia. He was discharged after 14 days in stable condition. Conclusions. COVID-19 infection can be complicated by DKA and development of DM in previously non-diabetic individuals. It is possible that SARS-CoV-2 may aggravate pancreatic beta cell function and precipitate DKA. Very few cases have been reported in the literature on COVID-19 infection precipitating DKA in a newly diagnosed patient of type 1 diabetes mellitus. Keywords: type 1 diabetes; diabetic ketoacidosis; COVID-19 pneumonia
Given positive contact history, he was tested and confirmed to be infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

He is non-smoker and has no family history of DM. Upon examination in the emergency room, he was conscious and oriented to time, place and person but looked dehydrated. He was febrile, but he did not display Kussmaul’s breathing. His respiratory rate was fluctuating 22–26/min, and $O_2$ saturation was 96% without $O_2$ therapy. His body mass index was 21.6 kg/m² with no signs of insulin resistance.

Laboratory investigations were significant for hyperglycaemia 479 mg/dL, high anion gap 26 mEq/L, metabolic acidosis: Base excess = $-23.2$ mEq/L; pH 7.140 and ketonuria $+3$ (150 md/dl), confirming the diagnosis of DKA.

The rest of his investigations showed the following:
- BUN: 51 mg/dl, normal range (10–50).
- Creatinine: 1.2 mg/dl, normal range (<1.3).
- SGPT = 20 U/l, normal range (0–46).
- Na: 129 mmol/l, normal range (135–145).
- K: 2.9 mmol/l, normal range (3.5–5.1).
- Cl: 95 mmol/l, normal range (98–107).
- S. lactate: 1.4 mmol/l normal range (0.5–1.1).
- CRP: 25.23 md/dl, normal range (< 10 mg/l Normal Range).
- WBC: 11.05 × 10^3/l, normal range (4–11).
- Lymphocytes: 12.1%; normal range (25–40%).
- Hgb: 14.1 gm/l, normal range (12–14).
- Platelets: 281 × 10^3/l, normal range (140–400).
- C-peptide 0.856 (ng/ml), normal range (0.8–7.6 ng/ml).
- Insulin 2.74 μIU/l, normal range (2.6–24.9 μIU/l).
- LDH: 792 unit/l, normal range (210–450).
- Ferritin: 1842 mg/dl, normal range (20–400).
- SGPT = 20 U/l; normal range (0–46).
- BUN: 51 mg/dl, normal range (10–50).
- Creatinine: 1.2 mg/dl, normal range (<1.3).
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- Hgb: 14.1 gm/l, normal range (12–14).
- Platelets: 281 × 10^3/l, normal range (140–400).
- Chest X-ray: showed bilateral infiltration.
- Chest CT: CO-RADS category 5; bilateral ground-glass opacities and crazy-paving pattern, 70% involvement of the lungs, CT severity score = 18/25.
- Insulin 2.74 μIU/l, normal range (2.6–24.9 μIU/l).
- C-peptide 0.856 (ng/ml), normal range (0.8–3.1 ng/ml).
- Anti GAD-IgG — Negative < 5 (< 10 Negative; > 10 Positive).
- HbA1c: 12.8%.
- Oronasal swab was positive for COVID-19 by real-time reverse transcription-polymerase chain reaction (rRT-PCR) test.

Urinalysis revealed 1000 mg/dl of glucose, 150 mg/dl of ketones and 30 mg/dl of protein.

Inflammatory markers:
- CRP: 25.23 md/l, normal range (< 10 mg/l Negative; > 10 mg/l Positive).
- LDH: 792 unit/l, normal range (210–450).
- Ferritin: 1842 mg/dl, normal range (20–400).
- D dimer: 1969 mg/dl, normal range (0–500).
- Platelets: 281 × 10^3/l, normal range (140–400).
- C-peptide 0.856 (ng/ml), normal range (0.8–7.6 ng/ml).
- Insulin 2.74 μIU/l, normal range (2.6–24.9 μIU/l).
- LDH: 792 unit/l, normal range (210–450).
- Ferritin: 1842 mg/dl, normal range (20–400).
- D dimer: 1969 mg/dl, normal range (0–500).

Cardiac evaluation:
- ECG normal sinus rhythm.
- Cardiac enzymes and troponin were normal.

In ED, he received 14 units IV regular insulin as a bolus and 1 litres of IV normal saline and started on DKA protocol with insulin infusion, IV fluids and potassium replacements. Serum electrolytes were closely monitored. DKA resolved after 24 hrs and he was transitioned to subcutaneous insulin therapy. He stayed in the hospital for 14 days and completed ten days course of antibiotics, Levofloxacin 500 mg and Meropenem 3 g. The day after admission he was assisted with oxygen therapy because her saturations fall to 86%.

He was managed with 20 litres high flow oxygen and 5 days course of dexamethason 4 mg, two times daily with a gradual decrease of doses. Fourteen days later he was weaned off Oxygen and he was discharged on insulin Aspart 6 UI before each meal and insulin Lantus 14 UI once daily. He was recommended to contact his local endocrinologist after four weeks, for the follow up consult.

Discussion

The patient in this case report was presented with two life threatening conditions, DKA and COVID-19 pneumonia. The prompt recognition and treatment of these conditions is crucial and resulted in good outcome.

DKA is a diabetic emergency and considered to be a common presentation of both T1DM and T2DM. It arise as a result of severe insulin deficiency, increased counter regulatory response which results in the production of ketones [8].

The most common trigger factors are prolonged uncontrolled blood sugar or acute stress including infection (pneumonia, urinary tract infection), acute myocardial infarction or cerebrovascular accident. Also alcohol abuse and drugs like SGLT-2 inhibitors [9] can precipitate an DKA episode.

The patient in this case report was presented with DKA and newly diagnosed T1DM triggered by COVID-19 pneumonia.

The underlying pathophysiology of new onset DM and its severe form DKA in patients with COVID-19 is still not well understood. Viral infection have been widely associated with T1DM pathogenesis.

T1DM is a genetic autoimmune condition where b-cells are destroyed by the auto-reactive CD4+ and CD8+ T cells causing insulin deficiency [10].

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), responsible for COVID-19, uses ACE2 receptor to bind and enter to infected cells as a viral complex [6].

Angiotensins converting enzyme (ACE) is the key enzyme in mediating the effects of rennin angiotensin aldosterone system (RAAS) by converting angiotensin I to II. The more recently identified to angiotensin I–VII, was found to be the functional receptor for SARS-CoV-1 and -2 [11].

ACE2 is abundantly present in humans in the epithelia of the lung and small intestine, which might provide possible routes of entry for the SARS-CoV-1 and -2 [12]. Study of 72 human tissues confirmed ACE2 mRNA expression in tissues other than the lung and gastrointestinal system, like testis, cardiovascular, renal, and pancreas [13, 14].

It was found that ACE2 is expressed in the endocrine part of the pancreas. This suggests that SARS coronavirus enters islets cells using ACE2 as its receptor and damages B-cell islets leading to insulin deficiency and development of acute DM [7].

This is supported by the findings of strong immunopositivity for ACE2 in pancreatic islets while exocrine tissues were only weakly positive [15]. Similarly, evidence in diabetic mice demonstrated that ACE2 activity levels were enhanced in the pancreas [15, 16].

In addition to the direct B cell injury, the expression of ACE2 on the surface of the pancreas is downregulated fol-
lowing endocytosis of the virus-ACE2 receptor complex. This in turn can lead to increased concentration of angiotensin II and inhibit insulin secretion [17]. These interactions between SARS-CoV-2 and RAAS might explain the underlying mechanism and pathophysiology of DKA.

All these pathophysiological events occurring simultaneously with inflammatory stress because of pulmonary infection might have contributed to the acute worsening of pancreatic beta cell function and precipitated DKA in this patient.

It remains to be investigated, whether this beta cell damage is transient or permanent.

Our understanding so far is uncertain if this new-onset diabetes is classic T1DM or some new form of DM.

The presentation of the patient in this case report is consistent with the hypothesis that COVID-19, not only causes hyperglycaemia and insulin resistance in patients known to be diabetic [3, 18], but can also predisposes newly diagnosed diabetes mellitus to DKA which can sometimes be resistant to treatment [19–21].

The development of diabetes and DKA can further complicate the course of COVID-19 infection. Diabetic patients with COVID-19 have worse prognosis than nondiabetics [1, 3].

This could be explained in part by high inflammatory and pro-coagulant state in diabetics including IL-6, C-reactive protein, serum ferritin, coagulation index, and D-dimer [2, 4, 22].

While hyperglycemia is seen to increase mortality and morbidity related to COVID-19, the virus itself can induce/ worsen hyperglycemia, culminating in a vicious cycle [23].

Conclusions

There are enough evidences to conclude that COVID-19 can lead to uncontrolled hyperglycaemia and the development of new onset diabetes mellitus which can further complicate the course and outcome of COVID-19 infection.

It is possible that SARS-CoV-2 may aggravate pancreatic beta cell function and precipitate diabetic ketoacidosis in patients with known or not known diabetes.

Patients with elevated blood sugar and no history of diabetes should be evaluated for the possibility of new onset diabetes mellitus and diabetic ketoacidosis, especially in the setting of concomitant COVID-19 infection.

Further studies and long term follow-up of children and adults presenting with new-onset diabetes during this pandemic is required to fully understand the type of diabetes induced by COVID-19 and to reveal the exact underlying pathophysiological mechanism of this serious condition.

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Diabetic ketoacidosis, precipitated by COVID-19, during the pandemic

The pandemic

Diabetes is a chronic disease that affects millions of people worldwide. The COVID-19 pandemic has had a significant impact on the management of diabetes, with increased hospitalizations and mortality rates in patients with diabetes. The aim of this study was to report a case of diabetic ketoacidosis precipitated by COVID-19 in a patient with newly diagnosed diabetes.

Case report

A 29-year-old male patient presented to our hospital with a 5-day history of fever, fatigue, and polyuria. His laboratory results showed a high level of blood glucose, metabolic acidosis, ketonuria, and diabetic ketoacidosis. Additionally, he tested positive for COVID-19, and his chest CT scan showed bilateral COVID-19 pneumonia (opacity, consolidation of lung pattern). He was successfully treated with intravenous fluids and insulin according to the protocol for diabetic ketoacidosis. He also received intravenous antibiotics, steroids, and oxygen therapy due to COVID-19 pneumonia. He was discharged in stable condition 14 days later.

Conclusions

COVID-19 infection may be complicated by diabetic ketoacidosis and the development of diabetes in previously healthy individuals. It is possible that SARS-CoV-2 causes beta-cell damage and the development of diabetic ketoacidosis. In the literature, there is a small number of cases where COVID-19 infection resulted in diabetic ketoacidosis in patients with newly diagnosed diabetes.

Keywords: diabetic ketoacidosis; COVID-19; pneumonia; diabetes type 1; diabetes type 2

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