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Short Communication

Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination

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Abstract

SARS-CoV-2 pandemic has claimed millions of lives since its first identification in December 2019. Patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, whereas infection itself can be associated with severe hyperglycemia, including hyperglycemic emergencies. While the accelerated vaccine development and rollout have considerably decreased morbidity and mortality with reasonable safety, there are emerging reports of worsening of hyperglycemia in response to vaccination, with possible shared pathophysiology with COVID-19 infection-related hyperglycemia. We hereby report two young patients with type 1 diabetes (T1DM) who presented with severe diabetic ketoacidosis (DKA) after receiving second doses of COVISHIELD (ChAdOx1 nCoV-19) and COVAXIN (BBV152- inactivated whole virion) vaccines. Though a causal link cannot be established, post-vaccination immune response can potentially explain this transient worsening of hyperglycemia and hyperglycemic emergencies. We, hence report diabetic ketoacidosis (DKA) following COVID-19 vaccination in T1DM. We suggest that people with diabetes, particularly patients with T1DM with inadequate glycemic control should ideally be closely monitored for hyperglycemia and ketonemia for at least 2 weeks after receiving vaccination for COVID 19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has emerged as the biggest health care crisis that has affected mankind in centuries. Initially identified as clusters of cases of pneumonia in Wuhan, China in December 2019, the infection rapidly spread beyond China. World health organization (WHO) declared the SARS-CoV-2 outbreak as a pandemic on the March 1, 2020. As of 2nd November 2021, there have been 246 million confirmed cases and 5 million deaths worldwide due to the pandemic, with India accounting for 4 million confirmed cases and 0.45 million deaths [1,2].

It has been demonstrated in multiple studies that diabetes has been associated with increased risk of severe disease, acute respiratory distress syndrome (ARDS), disease progression and increased mortality rates [3,4]. In fact, there exists a bidirectional relationship between SARS-CoV2 infection and diabetes, with infection being associated with worsening of hyperglycemia in preexisting diabetes and new-onset hyperglycemia [5].

The pandemic necessitated the rapid development of vaccines worldwide. The accelerated vaccine rollout has considerably reduced disease-related morbidity and mortality with reasonable safety. However, DKA/hyperosmolar hyperglycemic syndrome (HHS) post-vaccination for SARS CoV2 infection has been described in only a few case reports in the recent past. We hereby present two cases of young type 1 diabetes mellitus (T1DM) who presented with severe DKA within a week after receiving the second doses of the COVISHIELD (ChAdOx1 nCoV-19) and COVAXIN (BBV152- inactivated whole virion) vaccines for SARS CoV2.

2. Case series

2.1. Case 1

A 20 year old male, known case of T1DM since 6 years, presented with abdominal pain, decreased appetite and vomiting for 2 days. He was on premix insulin (Isophane insulin 70% and Human insulin...
Clinical and biochemical parameters of the two cases.

| Case 1 | Case 2 | Reference range |
|--------|--------|-----------------|
| Age (years) | 20 | 25 | – |
| Gender | Male | Female | – |
| Duration of T1DM | 6 years | 6 years | – |
| Details of vaccination | COVISHIELD (ChAdOx1 nCoV-19)- second dose | COVAXIN (BBV152- inactivated whole virion)- second dose | – |
| Time to symptoms after vaccination | 1 day | 4 days | – |
| Time to DKA after vaccination | 3 days | 6 days | – |
| Arterial blood gas analysis | | | |
| pH | 6.9 | 7.08 | 7.35–7.45 |
| HCO3 (mEq/L) | 2.5 | 7.4 | 22–26 |
| pCO2 (mm Hg) | 9.2 | 24.7 | 35–45 |
| Anion gap (mEq/L) | 33.79 | 15.3 | 8–12 |
| Serum β hydroxy butyrate (mmol/L) | 3.6 | 3.8 | <0.6 |
| Hemoglobin (g/dl) | 12.1 | 12.9 | 13–17 |
| Total leukocyte count (/μL) | 9850 | 34830 | 4000–10000 |
| Differential (%) | | | |
| Neutrophils | 73% | 84% | – |
| Lymphocytes | 19% | 10% | – |
| Monocytes | 6.6% | 6% | – |
| Eosinophils | 0.6% | 0% | – |
| Platelets (/μL) | 314000 | 481000 | 150000–400000 |
| Urea (mg/dl) | 51 | 52 | 17–43 |
| Creatinine (mg/dl) | 1.26 | 1.34 | Males: 0.84–1.25 |
| AST (IU/L) | 23 | 133 | Females: 0.66–1.09 |
| ALT (IU/L) | 23 | 23 | <35 |
| Total bilirubin (mg/dl) | 0.27 | 0.96 | 0.3–1.2 |
| Direct bilirubin (mg/dl) | 0.07 | 0.16 | <0.2 |
| Total protein (mg/dl) | 7.9 | 6.29 | 6.6–8.3 |
| Albumin (mg/dl) | 4.37 | 3.37 | 3.5–5.2 |
| Alkaline phosphatase (IU/L) | 184 | 126 | 30–120 |
| Serum sodium (mEq/L) | 131 | 133 | 136–146 |
| Serum potassium (mEq/L) | 3.3 | 3.51 | 3.5–5.1 |
| ESR (mm/h) | 1.08 | 31 | <20 |
| hsCRP (mg/L) | 14.1 | 16.3 | <1 |
| HbA1c (%) | 8 | 8.8–10.6 |
| Corrected calcium (mg/dl) | – | 2.1 | 2.5–4.5 |
| Phosphorus (mg/dl) | – | <4 | 30–100 |
| 25-(OH) vitamin D (ng/ml) | – | – | – |
| Urine routine microscopy | No pyuria | No pyuria | – |
| Chest X-ray | Normal | Normal | – |

AST: Aspartate transaminase, ALT: Alanine transaminase, ESR: Erythrocyte sedimentation rate, hsCRP: high sensitivity C-reactive protein.
insulin upon stabilization. She had neutrophil predominant leukocytosis at admission with raised inflammatory markers. She developed right-sided ear discharge 2 days after the hospital admission for DKA. A thorough ENT examination confirmed a tympanic membrane perforation with acute suppurative otitis media. Klebsiella pneumoniae was cultured from the ear swab. She was treated with piperacillin-tazobactam as per culture sensitivity, with which the discharge improved. The rapid antigen test for COVID-19 was negative. Hypokalemia and hypophosphatemia with severe vitamin D deficiency were found incidentally. The patient was asymptomatic for the same, and she was started on calcium and vitamin D supplements. Other relevant investigations were unremarkable and have been summarized in Table 1. She was discharged one week later on a subcutaneous basal-bolus regimen at a dose of 1.1 units/kg/day, and is doing well on OPD follow up.

3. Discussion

The COVID19 pandemic has led to the crippling of health care systems worldwide, cutting across nations and races. This led to the fast-tracking of vaccine development at a hitherto unseen pace, resulting in the development of multiple vaccines. As of 2nd November 2021, more than 7 billion doses of vaccines have since been administered worldwide [1].

India started the vaccination drive on January 16, 2021, and has since provided emergency authorization to three vaccines: the indigenously manufactured COVISHIELD (ChAdOx1 nCoV-19), the adenovirus vector-based vaccine developed with the master stock of ChAdOx1 nCoV-19 by Oxford–AstraZeneca, India’s first domestic vaccine- COVAXIN (BBV152- inactivated whole virion), an inactivated virus vaccine developed and manufactured by Bharat Biotech, and Sputnik V (Gam-COVID-Vac), a dual adenoviral vector-based vaccine developed by Gamaleya Research Institute of Epidemiology and Microbiology in Moscow, Russia [6,7]. More than 1.07 billion doses of vaccines have since been administered in India [8].

There exists a bidirectional relationship between diabetes and COVID-19. Diabetes is an independent predictor of worse outcomes in COVID-19 patients. The compromised innate immunity, an underlying chronic low-grade inflammation and an exaggerated pro-inflammatory response, characterized by increased cytokines like IL-1, IL-6, TNF-α, C-reactive protein, ferritin, and a hypercoagulable state contribute to the increasing severity in diabetics [9–11]. Acute hyperglycemia can upregulate angiotensin-converting enzyme 2 (ACE-2) expression facilitating viral entry, while chronic hyperglycemia can lead to low ACE-2 expression, leading to decreased degradation of angiotensin II to the vasodilatory, anti-proliferative and anti-inflammatory peptide angiotensin [11–7]. This response may be exaggerated after the immune response after natural infection or vaccination [12].

SARS-CoV-2 infection is also associated with an adverse effect on glycemia. Proposed mechanisms include islet cell damage and acute insulinopenia after cellular entry via pancreatic ACE-2 receptor [13], cytokine storm [5], oxidative stress, overactivation of the renin-angiotensin-aldosterone system (RAAS), and dysregulated release of stress hormones like cortisol and catecholamines leading to increased insulin resistance [10,14].

DKA and less commonly combined DKA/HHS have been well described in relation to COVID-19 infection. Type 2 DM comprises nearly 80% of the cases, probably reflective of the greater population prevalence, while T1DM and newly diagnosed DM constitute around 10% of the cases each. Acute β cell damage leading to acute insulinopenia and IL-6 mediated increased ketogenesis drive the pathogenesis of DKA [15].

Hyperglycemic emergencies after vaccination for SARS-CoV-2 infection, however, have been reported in only few publications to the best of our knowledge to date (26th November 2021, PubMed Search). Zilbermint et al. reported a case of severe DKA after receiving a second dose of mRNA-1273 Moderna vaccine in a 24-year-old female with T1DM. The in-hospital course was significant for transient high insulin requirements, suggestive of insulin resistance. There were no other identifiable DKA precipitants clinically or on investigations [16]. The similarities with our patients are the poor glycemic status, and presentation after the second dose of vaccine. Anecdotal self-reported surveys have also revealed elevated blood glucose in 14–18% of people after the first dose and 26–33% after the second dose in people with T1DM [17].

Abu-Rumaileh et al. [18] reported one patient of HHS, whereas Edwards et al. [19] and Lee et al. [20] each reported three patients of hyperglycemic emergencies respectively. These patients had pre-existing or newly diagnosed type 2 diabetes mellitus (T2DM), were older at presentation, had one or more features of metabolic syndrome and one patient had cardiovascular complications. They also presented with prominent osmotic symptoms, higher blood glucose values, consistent with clinical diagnoses of HHS or HHS-DKA. Acute kidney injury was reported in six of the seven reported patients.

Notably, all the patients reported by Abu-Rumaileh et al. [18] and Lee et al. [20] could be transitioned to oral hypoglycemic agents on outpatient follow-up after the initial intravenous fluid and insulin therapy. C-peptide recovery was documented in three patients, further supporting the hypothesis of recovery of β cells and insulinopenia after the acute hyperglycemic emergency. Pertinent differences in the presentation from our cases have been summarized in Table 2.

Besides these reports, Mishra et al. reported 3 cases of type 2 diabetes with transient worsening of hyperglycemia after receiving the first doses of COVISHIELD (ChAdOx1 nCoV-19) vaccine [21]. Hyperglycemia was exacerbated 1–6 days after the dose and lasted for 3–30 days, with one patient requiring an increased dose of oral medications. None of the patients required intensive treatment. This mild and transient exacerbation was hypothesized to be due to the post-vaccine inflammation and immune response.

On the contrary, our patients were younger, with T1DM presenting with severe DKA after receiving second doses of the COVISHIELD (ChAdOx1 nCoV-19) and COVAXIN (BBV152- inactivated whole virion) respectively. However, one potentially confounding factor was the presence of acute suppurative otitis media in the second patient as a simultaneous precipitating factor, however, the onset of symptoms after admission does not correlate temporally with the onset of DKA.

The virtually non-existent β cell reserve in T1DM confers a higher risk of DKA as opposed to HHS, and this risk is amplified by COVID-19 infection via direct virus-mediated and cytokine-mediated adverse effects on glycemia. In addition, the extreme glycemic excursions in T1DM may pose a higher risk of oxidative stress via increased activation of protein kinase C and production of advanced glycation end products, resulting in a self-perpetuating cycle and worsening of hyperglycemia [22].

Immune-response mediated hyperglycemia is more likely to be the mechanism for post-vaccination hyperglycemic emergencies, in contrast to the contribution of direct virus-mediated effects in COVID-19 infection-related hyperglycemia. This is further supported by the fact that DKA was precipitated after the 2nd dose of respective vaccines, which might be due to a more robust immune response after the second dose. Another possibility is a reaction to specific excipients in the vaccine formulation. However, the fact that our patients received two different vaccines makes this an unlikely scenario. This is further supported by the fact that the cases reported so far have occurred in association with at least 3 different vaccines- Moderna (mRNA-1273) (n = 3), Pfizer-BioNTech
(BNT162b2 mRNA vaccine) \((n = 2)\), and ChAdOx1 nCoV-19 \((n = 3)\); making vector, mRNA or excipient related mechanisms unlikely.

Another important finding is the uniformly poor glyemic status in all the reported cases, with HbA1c > 12%. This might reflect the tendency of uncontrolled diabetes to amplify the inflammatory response and oxidative stress, precipitating diabetic ketoacidosis. This is also supported by the fact that inflammatory markers were elevated in both of our patients after vaccination. The mild increase in insulin requirements seen during admission in our patients is possibly due to the ongoing exaggerated immune response to vaccination and ketoacidosis.

Hence, in the absence of other precipitating factors, it is possible that the DKA was precipitated by vaccination in these patients, who were at high risk in view of poorly controlled diabetes. In fact, our case 1 already had a DKA 9 months back, suggesting poor long-term glyemic control. This underlines the importance of monitoring for worsening of hyperglycemia as well as ketones to identify DKA at the earliest in T1DM patients for at least 1–2 weeks after vaccination, specifically in patients with inadequate glyemic control. The possibility of vaccination precipitating DKA should therefore be considered after ruling out more common precipitants like non-compliance and infections. Vaccine manufacturers and healthcare authorities should be vigilant for this rare, but potentially life-threatening adverse effect. However, this does not take away from the fact that vaccines are the single most important preventive measure in curbing the spread of COVID-19 and the resultant healthcare costs, and all efforts must be made to continue vaccination drives on a war footing.

**Author’s contribution**

AR conceived the idea. VG, PJ, AR, MM were involved in the clinical care. AR, VG and PJ did the literature search and VG, PJ drafted the manuscript. AR, MM, RS, MKG revised the manuscript with critical suggestions. All authors have read and approved the final version of the manuscript.

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Table 2

Comparison of pertinent characteristics of our cases vis-à-vis previously reported cases.

| Gender | Age (years) | Type of diabetes | Vaccine type and dose | Time to presentation after vaccination | Diagnosis | HbA1c | Comorbidities |
|--------|-------------|------------------|-----------------------|---------------------------------------|-----------|-------|--------------|
| Male   | 20          | T1DM             | COVISHIELD (ChAdOx1 nCoV-19)- second dose | 3 days                               | Severe DKA | 14.1% | –            |
| Female | 25          | T1DM             | COVAXIN (BBV152- inactivated whole virus)- second dose | 6 days                               | Severe DKA | 16.3% | –            |
| Male   | 53          | T1DM             | Moderna (mRNA-1273)- second dose | 15 h (symptom onset) | Severe DKA | 12%  | Overweight   |
| Male   | 58          | T2DM             | Pfizer-BioNTech (BNT162b2)- second dose | 6 days                               | HHS       | 13%  | Hypertension |
| Male   | 60          | T2DM             | ChAdOx1 nCoV-19- first dose | 21 days                               | Hyperglycemic ketosis | 14.1% | Hypertension Hypercholesterolemia |
| Male   | 59          | T2DM             | ChAdOx1 nCoV-19- first dose | 36 days                               | HHS/DKA/HHS | 14.7% | Hypothyroidism |
| Male   | 53          | T2DM             | ChAdOx1 nCoV-19- first dose | 20 days                               | Predominant DKA | 17.1% | –            |
| Male   | 52          | T2DM             | Pfizer-BioNTech (BNT162b2)- first dose | 3 days                               | HHS       | 12%  | Hypertension, obesity |
| Male   | 60          | T2DM             | Moderna (mRNA-1273)- first dose | 2 days                               | HHS       | 13.2% | Hypertension, overweight |
| Male   | 87          | T2DM             | Moderna (mRNA-1273)- first dose | 10 days                               | HHS/DKA | – | Hypertension Hyperlipidemia Ischemic stroke Congestive heart failure |

**Declaration of competing interest**

None.

**Abbreviations:**

ACE-2 Angiotensin-converting enzyme-2
ARDs acute respiratory distress syndrome
CRP C-reactive protein
DKA Diabetic ketoacidosis
HHS Hyperosmolar hyperglycemic syndrome
IL Interleukin
RAAS Renin-angiotensin-aldosterone system
RT-PCR Reverse transcriptase polymerase chain reaction
SARS-CoV2 severe acute respiratory syndrome coronavirus 2
TNF α Tumor necrosis factor α
WHO World health organization

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