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Case Report

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# New Onset of Type 1 Diabetes Mellitus Post-COVID-19 Vaccine

Khaled H. Aburisheh[a, c], Hamza M.K. Enabi[b], Nora A. Alodah[b], Bassam H. Alotary[b], Linah A. Algheryafi[b], Ayman M. Almairi[b], Amani A. Aldhewaila[a]

## Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with an increased morbidity and mortality worldwide. Coronavirus disease 2019 (COVID-19) vaccines have shown high efficacy in preventing the infection but with many possible side effects such as hyperglycemia. New-onset diabetes mellitus (DM) and severe metabolic complications have been reported post-vaccination. Here we report a 45-year-old woman who came to the hospital complaining of polyurea, polydipsia, and weight loss 3 weeks after the first activation dose of COVID-19 vaccine. Her hemoglobin A1c (HbA1c) upon presentation was 9% without any prior history of DM. She was diagnosed with type 1 diabetes mellitus (T1DM), as the anti-glutamic acid decarboxylase (GAD) antibody was positive and complicated during follow-up with diabetic ketoacidosis (DKA). This is the first case in Saudi Arabia suggesting that the COVID-19 RNA-based vaccines might cause new onset of T1DM, complicated by late DKA.

**Keywords:** COVID-19; SARS-CoV-2; mRNA vaccine; Hyperglycemia; Type 1 diabetes mellitus

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) have afflicted 768 million people in a worldwide pandemic since its first case was reported in Wuhan (China) in December 2019. With deaths - as per the World Health Organization numbers in July 2023 - reaching 6.9 million [1], the discovery of an effective vaccine against COVID-19 was a critical step in the fight against the epidemic [2, 3]. Classifications of approved vaccines eligible for clinical trials include inactivated vaccines, live attenuated, vector, RNA, DNA, protein subunit, and virus-like particle (VLP) vaccines [4]. Those vaccines have been administered with high efficacy and safety [4, 5].

However, as the administration of the COVID-19 vaccine progressed, the possibility of side effects was addressed ranging from most common but mild events such as injection site pain, headache, fatigue, fever, myalgia, joint pain, and lymphadenopathy to rare but serious events like arrhythmia, carditis, thrombosis, convulsions, thrombocytopenia, and Guillain-Barre syndrome [6]. Moreover, the development of new-onset diseases such as autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis, or the worsening of patients' illnesses like poor glycemic control post-vaccination has been reported [7, 8].

Diabetes mellitus (DM) is considered a risk factor contributing to the severity and mortality of the infection; in contrast, new-onset DM and severe metabolic complications including diabetic ketoacidosis (DKA) and hyperosmolarity have also been observed in patients with COVID-19 [9, 10]. Moreover, it was reported that the COVID-19 vaccine was associated with the development of new onset of type 1 diabetes mellitus (T1DM) [11] and diabetic emergencies in those with a history of DM [8]. We report the first case in Saudi Arabia of newly diagnosed T1DM with positive autoantibodies following the first activation dose vaccine in a previously healthy subject which was complicated later by DKA.

## Case Report

### Investigations

A 45-year-old woman presented to the emergency department at a tertiary hospital in Saudi Arabia as a case of severe hyperglycemia with osmotic symptoms which started 3 weeks after the administration of the first activation dose of COVID-19 RNA-based vaccine (BNT162b2, Pfizer-BioNTech). When she first presented to the hospital, she was on oral paracetamol and topical diclofenac (Voltaren). She denied any immediate reactions after vaccine injection. She also disclaimed previous history of DM or COVID-19 infection. Her surgical history is significant for appendectomy and para-umbilical hernia repair

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[a]University Diabetes Center, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[b]Alfaisal University, Riyadh, Saudi Arabia
[c]Corresponding Author: Khaled Hani Aburisheh, University Diabetes Center, King Saud University Medical City, King Saud University, PO Box 11472, Riyadh 7805, Saudi Arabia. Email: kaburisheh@ksu.edu.sa

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with mesh 1 year ago. She has a paternal family history of type 2 diabetes mellitus (T2DM). She did not have any signs or symptoms of DKA. She was conscious and her oral temperature was 36.8 °C. Her respiratory rate was 19/min and her blood pressure was 124/74 mm Hg. Oxygen saturation was 97%. Her height, weight, and body mass index were 160 cm, 70 kg, and 27.34 kg/m$^2$, respectively. Upon investigation, random blood sugar was 31.9 mmol/L (reference range: < 11.1 mmol/L) and venous blood gas (VBG) analysis showed no ketosis or ketoacidosis with normal pH (7.36) and anion gap (11.5 mEq/L). She was discharged without any treatment and advised to follow up in primary care clinics for further management of diabetes.

After 1 week, she presented to her private clinic with polyuria, polydipsia, and weight loss. Her investigations showed hemoglobin A1c (HbA1c) of 9%, and thus she was given gliclazide 30 mg daily, metformin 500 mg daily, and sitagliptin 100 mg daily. Adding on, the patient's HbA1c level was repeated after 2 weeks which showed even higher levels of 11.9%, therefore, gliclazide dose was increased to 120 mg once daily.

After 1 week of increasing gliclazide dose, she presented to Diabetes Clinic at the University Diabetes Center, King Saud University Medical City, Riyadh, Saudi Arabia, with persistent severe hyperglycemia where her average blood sugar reading reached above 300 mg/dL. Insulin glargine 12 units daily was added, and further laboratory investigations were requested.

### Diagnosis

During follow-up, HbA1c was 10.8%, fasting blood glucose was 15.74 mmol/L, fasting C-peptide was less than 0.5 nmol/L, anti-glutamic acid decarboxylase (GAD) antibody level was positive (330.7 IU/mL), but anti-islet cells antibody and anti-zinc transporter 8 antibody were both negative (Table 1).

### Treatment

Oral hypoglycemic agents were stopped, aspart insulin was added, and insulin doses were adjusted according to her blood sugar readings. Three months after initiating insulin therapy, her HbA1c level reached 7.5% with interstitial glucose using flash glucose monitoring, time in the range (70 - 180 mg/dL) was 50% (target ≥ 70%) and time below the range (less than 70 mg/dL) was 5% (target < 7%). Her insulin dose was reduced accordingly.

Five months after the previous follow-up visit, she presented with uncontrolled DM, depressed mood, painful peripheral neuropathy, and no signs of hypoglycemia. She mentioned that she was not compliant with her diet or exercise. Therefore, escitalopram was added to her medication and the dose of glargine 300 was increased.

### Follow-up and outcomes

During follow-up after 3 months, she presented with insomnia and was referred to behavior therapy before presenting again within 1 month with the same complaint of insomnia in addition to low mood, fatigue, and loss of interest for which she was given mirtazapine 15 mg daily.

**Table 1.** Laboratory Findings

| Assessment | Results | Reference ranges |
|---|---|---|
| Fasting glucose, mmol/L | 15.74 | 4.07 - 5.83 |
| Hemoglobin A1c, % | 10.8 | 4 - 6 |
| Fasting C-peptide, nmol/L | < 0.5 | 0.16 - 1.68 |
| Urea, mmol/L | 3.6 | 2.5 - 6.4 |
| Creatinine, mmol/L | 52 | 53 - 115 |
| Sodium, mmol/L | 139 | 136 - 145 |
| Potassium, mmol/L | 4.3 | 3.5 - 5.1 |
| TSH, mIU/L | 3.336 | 0.25 - 5 |
| Free T4, pmol/L | 15.2 | 11.5 - 22.7 |
| Anti-GAD antibody, IU/mL | 330.7 | < 10 |
| Anti-islet cells antibody, U/mL | 27 | < 28 |
| Anti-ZnT8 antibody, U/mL | 2 | < 15 |
| Insulin autoantibody, U/mL | < 0.4 | < 0.4 |

TSH: thyroid-stimulating hormone; GAD: glutamic acid decarboxylase; ZnT8: zinc transporter 8.

Lastly, the patient was admitted as a case of DKA after around 1 year of the diagnosis. She came to the hospital with mild abdominal pain that started the day before the presentation, mainly in the epigastric area with no radiation, and associated with nausea. According to the patient, she measured her blood glucose multiple times at home with persistent high readings. She was not compliant with her medications. Random blood sugar was 32.46 mmol/L. VBG analysis confirmed the diagnosis of DKA as pH was 7.189, bicarbonate was 12.3 mmol/L, and anion gap was 26.4 mEq/L. Urine ketone was +4 (≥ 150 mg/dL). DKA was well managed during admission which resolved, and she was discharged on glargine insulin 34 units daily with aspart insulin 14 units pre-meals.

## Discussion

We report the first case in Saudi Arabia of a healthy middle-aged woman newly diagnosed with T1DM after receiving the first activation dose of the Pfizer COVID-19 vaccine. She had a family history of T2DM and presented initially with mild symptoms of hyperglycemia managed initially with oral hypoglycemia agents, which shifted to insulin therapy due to persistent hyperglycemia, and complicated later with DKA.

During the COVID-19 outbreak, the reduction of hospitalization and mortality has been a crucial issue that has prompted the development of vaccines. As a result, two messenger RNA (mRNA)-based SARS-CoV-2 vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), were developed in a short time. These vaccines have demonstrated high efficacy in preventing infection with the virus [12].

Accumulating cases of acute hyperglycemia or new-onset DM have been reported in patients following COVID-19 infection, some of which include cases of autoimmune DM [13]. Such findings suggest that COVID-19 infection induces the activation of autoimmunity associated with T1DM [14]. Therefore, it is suggested that the vaccine also could induce autoimmune DM [15].

Our case is similar to a case reported by Moon et al which is considered the first case of diagnosing T1DM post-COVID-19 vaccination without DKA. However, the patient received the Moderna vaccine as the second dose in comparison to our case that received the third dose of the Pfizer vaccine [16].

Given that the presenting HbA1c in our case was 9%, which was 3 weeks after receiving the vaccine, it is speculated that the hyperglycemia process started soon after the vaccination. This has been shown in many reported cases previously [17-19].

Abu-Rumaileh et al reported a case of developed T2DM 3 weeks post-vaccination who had a family history of T2DM. They believe that the vaccine shows up the patient's prediabetes [17]. Moreover, Patrizio et al published a case with a history of T2DM and converted to autoimmune diabetes after receiving the vaccine [18]. In contrast, we could not rule out the presence of preexisting undiagnosed diabetes in our case, which could be considered due to the presence of a family history of T2DM and the high initial HbA1c.

Genetic susceptibility was tested and confirmed the genetic predisposition to T1DM in those who developed the disease post-vaccination in many reported cases [19-21]. However, we did not analyze human leukocyte antigen (HLA) class II genotyping; in our case, T1DM was confirmed with positive anti-GAD antibodies and low C-peptide. In contrast, islet-related autoantibodies were all negative in a previously reported case [22].

Sakurai et al reported the first case of new-onset fulminant T1DM 8 days after the Pfizer vaccine, which presented with early DKA [21], in comparison to our case where she developed T1DM 3 weeks after the vaccine but complicated with late DKA around 1 year after the diagnosis.

The causal relationship between COVID-19 vaccine and autoimmune disease is still unclear; however, many possible mechanisms could summarize it. Molecular mimicry is one of the mechanisms where there is an immune cross-reaction between human proteins and vaccine elements. The adjuvants in vaccines are also suggested to trigger immune-mediated diseases and the concept called autoimmune/inflammatory syndrome induced by adjuvants (ASIA). However, this concept needs to be confirmed by more studies as two large human clinical trials refuted the ASIA concept and showed no increase in incidence or exacerbation of autoimmune disease after receiving aluminum-containing vaccine/allergen-specific immunotherapy in contrast to the case series that suggested the ASIA. Furthermore, the board criteria of ASIA, which lose precision, result in difficulty in applying and interpreting them in clinical practice. Another suggested mechanism is that cytokines like interferon I could activate T and B cells and promote long-term memory carried by $CD8^+$ cells in a process called bystander activation. Melanoma differentiation-associated protein 5 (MDA5) is an intracellular viral sensor protein that interacts with viral RNA to trigger the production of interferon I. This response was suggested to interfere with B-cell function and lead to the development of hyperglycemia, which is the most relevant hypothesis in this case [7, 15, 23, 24].

### Conclusion

COVID-19 vaccines were developed in a very short time resulting in documented adverse effects including vaccination-induced hyperglycemia. We report the first case in Saudi Arabia of a patient who developed new-onset DM following COVID-19 vaccination, with typical diabetic symptoms such as polyurea and polydipsia. This could suggest the possibility of COVID-19 RNA-based vaccines triggering T1DM with no prior history of hyperglycemia; however, further large-scale case-control and molecular-level studies are desired to demonstrate the causality between them and the biological plausibility of the effect.

### Learning points

We would like to highlight that COVID-19 vaccination could provoke adult-onset T1DM in those subjects without a history of diabetes. However, it is important to note that there is a lack of conclusive evidence of the relationship between the vaccine and the incidence of T1DM; many published case reports suggested this relationship, including ours. T1DM should be surveyed carefully after the vaccination. For patients with hyperglycemia post-vaccination, even in the absence of DKA, we suggest considering C-peptide, autoantibodies, and genetic testing.

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## Financial Disclosure

None to declare.

## Conflict of Interest

The authors declare that there is no potential conflict of interest relevant to this article.

## Informed Consent

Informed consent was taken from the patient.

## Author Contributions

Conceptualization: KHA, HME and AAA. Literacy search: NAA, BHA, LAA and AMA. Writing the initial draft: HME, NAA, BHA, LAA and AMA. Critical review and revision of

the initial draft: KHA and AAA. Supervision: KHA. All the authors read and approved the final manuscript.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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