AACE Clinical Case Rep. 10 (2024) 179–183

Clinical Case Reports™
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Case Report

Type 1 Diabetes Mellitus Caused by COVID-19 mRNA Vaccination: A Case Report and Literature Review of 17 Published Cases

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ARTICLE INFO

Article history:
Received 5 March 2024
Received in revised form
19 May 2024
Accepted 10 June 2024
Available online 13 June 2024

Key words:
SARS-CoV-2
insulin dependent
molecular mimicry
HbA1c

ABSTRACT

Background/Objective: Multiple cases of postvaccination immune-related adverse events have been reported. We, hereby, present a patient who presented with new-onset type 1 diabetes mellitus (DM) after COVID-19 messenger RNA (mRNA) vaccination.
Case Report: A 38-year-old Caucasian man presented with sudden onset of polyuria, polydipsia, and blurry vision for 1 month. The patient received the second dose of the COVID-19 mRNA vaccine (Pfizer-BioNTech) 4 weeks prior to symptom onset. Initial workup revealed glucosuria and hemoglobin A1c of 9.4%. Antibodies against multiple pancreatic beta cell autoantigens were detected. The patient was then initiated on insulin.
Discussion: Hypothesized mechanisms for development of type 1 DM after COVID-19 mRNA vaccination include molecular mimicry, autoimmune/inflammatory syndrome induced by adjuvants, and possible interaction between the angiotensin-I converting enzyme-2 receptor on beta cells and viral mRNA. An initial high index of suspicion should be accompanied by early autoantibody testing and initiation of insulin, if indicated. Finally, if diagnosed with type 1 diabetes, patients must have long-term follow-up as there may be brief periods where glycemic control is maintained off insulin.
Conclusion: New-onset type 1 DM has been reported after COVID mRNA vaccination. Clinicians should maintain a high index of suspicion and pursue early testing for the same to reduce adverse outcomes and improve long-term prognosis.

Introduction

Flexibility to respond to new variants and simple production process have made messenger RNA (mRNA) vaccines an effective and economical intervention to prevent infection in the COVID-19 pandemic. The most common adverse effects of SARS-CoV-2 vaccination are injection site reactions, fatigue, and headaches; however, multiple cases of postvaccination immune-related adverse events have been reported.[1,2] These adverse events cover a wide spectrum including myocarditis, transverse myelitis, multiple endocrinopathies, vasculitides, malabsorption syndromes, and rheumatologic disorders.[1,2]

While COVID-19 induced type 1A diabetes mellitus (DM) has been documented in literature,[3] recent reports have also described new-onset diabetes after COVID-19 mRNA vaccination.[4-7] This warrants further investigation for a possible pathophysiological link between these 2 apparently distinct disease processes.

Here, we report a patient who developed new-onset type 1 DM 4 weeks after the second dose of mRNA COVID-19 vaccine. We also review prior reports of COVID vaccination related type 1 diabetes and discuss demographic trends, clinical course, and future implications of this rare albeit significant adverse effect.

Case Report

A 38-year-old Caucasian man presented with a sudden onset of polyuria, polydipsia, and blurry vision for the past month. He had

Abbreviations: DM, diabetes mellitus; GAD-65, glutamic acid decarboxylase; HbA1c, hemoglobin A1c; mRNA, messenger RNA.

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https://doi.org/10.1016/j.aace.2024.06.001

also unintentionally lost 10 lbs in the same time frame. There was no family history of autoimmune disorders or diabetes. The patient received 2 doses of the mRNA COVID-19 vaccine (Pfizer-BioNTech), 3 weeks apart, with the second dose being about 4 weeks prior to symptom onset. The patient had a healthy lifestyle including daily exercise and a body mass index of 24.6 kg/m^2. He was not taking any medications or supplements at the time of diagnosis. Initial workup revealed hyperglycemia (random serum glucose 285 mg/dL) and hemoglobin A1c (HbA1c) of 9.4%, higher than the most recent HbA1c of 5.4% 6 months ago. Urinalysis was remarkable for glucosuria without ketonuria. Given the acute onset of DM, there was high concern for latent autoimmune diabetes in adult and the patient was started on insulin. Autoantibody testing revealed elevated titers of antibodies against zinc transporter ZnT8 (>500 U/mL, ref <15 U/mL), insulinoma-associated protein 2 (1.13 nmol/L, ref ≤0.02 nmol/L), and glutamic acid decarboxylase (GAD-65) (0.07 nmol/L, ref ≤0.02 nmol/L), but not to insulin (undetectable). No structural pancreatic pathology was noted on a computed tomography scan of the abdomen.

The patient used insulin for a few weeks (glargine 12 U daily and aspart 2 U 3 times daily). However, at the same time, he made further lifestyle modifications with increased intense daily exercise and a very strict low carbohydrate diet, and noted his home glucose readings were within normal range even off insulin. Thereafter, he self-discontinued insulin. Repeat HbA1c 3 months later was 5.2%. He was stable off insulin for 2 months, but had to be placed back on it for persistent hyperglycemia. Additional testing for a concomitant celiac disease or thyroid disorder was negative. Fasting C-peptide was low (0.6 ng/mL [0.2 nmol/L]). Repeat autoantibody testing showed persistently positive GAD-65, insulinoma-associated protein 2 and ZnT8 antibodies with additional anti-insulin antibodies. He continues to be on insulin degludec 14 U daily and insulin aspart 2 to 4 U with meals.

Discussion

Here, we report a case of a male patient presenting with new-onset type 1 DM after a recent mRNA COVID-19 vaccination with evidence of auto-antibodies against pancreatic beta cell antigens, who was thereafter treated with insulin. Although the development of type 1 DM was noted after vaccination, it is hard to establish whether the vaccine is causative or merely coincidental.

As part of our review, a comprehensive search of literature was conducted on PubMed using the keywords “COVID-19 vaccin*,” “SARS-CoV-2 vaccin*,” and “type 1 diabetes.” Initial search yielded 20 results. After manual review of the results, 14 full-text reports were retrieved,[4-17] and the 6 were excluded based on article type, study design, study population, or use of non-mRNA COVID-19 vaccine. The results of our search have been summarized in Table. These 14 reports include a total of 17 patients from 6 countries, with most being from Japan,[7-9,12,14-17] followed by Turkey,[6] Italy,[11,13] Korea,[4] Taiwan,[5] and United States.[10] The age at presentation ranged from 27 to 73 years (median 51 years [IQR 41-60]) and most patients were of Asian ethnicity (82.3%, $n = 14/17$). Most patients (76.5%, $n = 13/17$) received 2 doses of a mRNA COVID-19 vaccine before onset of symptoms. The timeline of symptom onset ranged from 1 day to 15 weeks after the most recent dose of mRNA vaccine. While most patients presented with polyuria, polydipsia, and weight loss (58.8%, $n = 10/17$), a significant number of patients also had diabetic ketoacidosis as part of their initial presentation (58.8%, $n = 10/17$). Twelve of these patients (70.6%) had detectable antibodies against pancreatic beta cell antigens, whereas 5 (29.4%) did not. Interestingly, 5 (29.4%) of the patients[7-9,12,15] underwent human leukocyte antigens typing and were noted to have a type 1 DM susceptible genotype. Similar to our patient, all of these patients were managed with insulin and most of them continued to be on insulin on outpatient follow-up.

Highlights

- New-onset type 1 diabetes mellitus has been reported after COVID mRNA vaccination.
- Possible mechanisms include molecular mimicry and interaction with pancreas receptors.
- There may be brief periods where glycemic control is maintained off insulin.

Clinical Relevance

We describe the diagnosis and management of a 38-year-old man who presented with new-onset type 1 diabetes mellitus after COVID-19 mRNA vaccination. This case serves as a reminder of the significance of an initial high index of suspicion in diagnosing rare postvaccination immune-related adverse events.

The pathogenesis of type 1A DM has been attributed to genetic susceptibility triggered by environmental agents such as viral infections, childhood immunization, and treatment with immune checkpoint inhibitor therapy. Several hypotheses have been proposed for development of type 1 DM after COVID-19 mRNA vaccination. First, molecular mimicry between SARS-CoV-2 peptide antigens and the human proteins may be responsible for cross-reactive interactions. In a recent study, Vojdani et al[18] reported significant cross reactivity between human anti-SARS-CoV-2 spike protein and nucleoprotein antibodies and multiple human target proteins, including GAD-65 antigen. Second, adjuvants included in the vaccine have been implicated in the pathogenesis of type 1 DM, as part of autoimmune/inflammatory syndrome induced by adjuvants. In addition to the COVID-19 mRNA vaccine, autoimmune type 1 DM has been reported after Vaxzevria (AstraZeneca),[11] hepatitis B virus (11 cases), and human papillomavirus vaccine (2 cases).[19] Third, the angiotensin-I converting enzyme-2 receptor that is involved in the SARS-CoV-2 interaction with the host cells may also play an important role. Given the angiotensin-I converting enzyme-2 expression on the pancreatic beta cells, SARS-CoV-2 infection can induce beta cell apoptosis.[20] This mechanism that has been postulated to be responsible for the higher risk of diabetes noted after a COVID-19 infection, which itself is poorly understood.[3] Similar mechanisms may be triggered by the COVID-19 mRNA vaccination. In addition to diabetes, COVID-19 vaccine-induced endocrine disturbances such as thyroiditis, Graves disease, hypophysitis and adrenal insufficiency have been reported.[1] There is growing literature about nonendocrine autoimmune conditions such as immune thrombocytopenia, vasculitis, Guillain-Barré syndrome, celiac disease and inflammatory arthritis, being triggered by the COVID-19 vaccination,[2] including both mRNA vaccines as well as adenovirus vector vaccines.

The observations from our case and review of literature have certain important implications for the management of individuals who receive a COVID-19 mRNA vaccine. First, universal guidelines for screening for prediabetes and diabetes must be followed to establish baseline glycemic control prior to COVID-19 vaccination. The American Diabetes Association, the American Association of Clinical Endocrinology, and the U.S. Preventive Services Task Force recommend screening for diabetes every 3 years in individuals with normal blood glucose levels. Second, clinicians must maintain a high index of suspicion for patients presenting with signs and

Table
Published Reports on Patients With New-Onset Type 1 Diabetes Mellitus After COVID-19 mRNA Vaccination

Author and country of publication	Demographic information	mRNA vaccine(s)	Timeline	Presentation	Workup	Clinical course/follow-up
Evidence of autoimmunity present						
Moon et al[4] (2023) Korea	56 y/F Asian	Moderna (2 doses)	2 mo after second dose.	Polyuria, polydipsia, and weight loss	HbA1c 11% Fasting C-peptide initially normal, but low later. Anti-GAD Ab present	Discharged on insulin with persistent insulin dependence at 5 wk postdischarge.
Lin et al[5] (2022) Taiwan	39 y/F Asian	Medigen (2 doses, spike protein vaccine) followed by Pfizer-BioNTech booster 8 mo later	14 wk after booster.	DKA	HbA1c 6.4%. Fasting C-peptide undetectable. Anti-GAD, anti-IA2 Ab present.	Discharged on long-term insulin with persistent insulin dependence at 3 mo postdischarge.
Yano et al[8] (2022) Japan	51 y/F Asian	Moderna (2 doses).	28 d after first dose. Second dose was 2 d after onset of symptoms.	Initially polyuria, polydipsia, and weight loss. Hospitalized with DKA 2 wk later.	HbA1c 10.3% (5.6% 3 mo ago) Fasting C-peptide normal. Positive anti-insulin, anti-TPO, and antithyroglobulin Ab.	Discharged on insulin. No follow-up information.
Kobayashi et al[9] (2022) Japan	59 y/M Asian	Pfizer-BioNTech (2 doses)	15 wk after second dose	DKA	HbA1c 7.8%. Fasting C-peptide undetectable. Anti-GAD, anti-TPO, antithyroglobulin Ab present.	Discharged on long-term insulin. Negative conversion of anti-GAD Ab after 45-d.
Aydoğan et al[6] (2022) Turkey	56 y/M Asian	Pfizer-BioNTech (2 doses)	15 d after second dose	Polyuria, polydipsia, and weight loss	HbA1c 8.2% (5.9% 6 mo ago) Fasting C-peptide normal Anti-GAD Ab detected.	Discharged on insulin. Gradual decline in insulin requirements followed by discontinuation at 3-mo follow-up.
	48 y/M Asian	Pfizer-BioNTech (2 doses)	2 mo after second dose	Fatigue	HbA1c 10.1% (5.6% 3 mo ago) Fasting C-peptide low Anti-GAD Ab detected.	Patient refused insulin. Received nutrition therapy.
	27 y/F Asian	Pfizer-BioNTech (2 doses)	3 wk after second dose	Polyuria, polydipsia, weight loss, blurry vision, and vaginal candidiasis	HbA1c 12.5% Fasting C-peptide low Anti-GAD Ab detected.	Gradual decline in insulin requirements with discontinuation of insulin.
	36 y/M Asian	CoronaVac (2 doses) followed by Pfizer-BioNTech (2 doses)	3 wk after second dose of Pfizer	DKA	HbA1c 12.6% Fasting C-peptide low Anti-GAD Ab detected.	Discharged on basal-bolus insulin, with reduction to basal-only insulin at 2 mo.
Kshetree et al[10] (2022) USA	69 y/M	mRNA vaccination followed by booster	2 mo after booster	Polyuria, polydipsia, blurry vision, weight loss followed by DKA 3 wk later.	HbA1c 13.7% Fasting C-peptide low Anti-GAD Ab detected.	Discharged on long-term insulin. Persistent insulin requirements at 3-wk follow-up.
Bleve et al[11] (2022) Italy	61 y/F Caucasian	Pfizer-BioNTech (2 doses)	1 d after second dose	Polyuria, polydipsia, and asthenia followed by DKA 26 d later.	HbA1c 11.5%. Anti-GAD and anti-TPO Ab detected.	Discharged on insulin. No follow-up information.
Sasaki et al[12] (2022) Japan	73 y/F Asian	Moderna (2 doses)	7 wk after second dose	Anorexia, fatigue, nausea/vomiting	HbA1c 9.3% Fasting C-peptide normal. Anti-GAD, anti-insulin Ab detected.	Discharged on insulin, with persistent dependence at 12-wk follow-up.
Patrizio et al[13] (2021) Italy	52 y/M	Pfizer-BioNTech (2 doses)	4 wk after second dose	Weight loss, asthenia	HbA1c 8.7% C-peptide low. Anti-GAD, antithyroglobulin, thyrotropin receptor Ab positive.	Treated with insulin. No follow-up information.
Present report (2023) USA	38 y/M Caucasian	Pfizer-BioNTech (2 doses)	4 wk after second dose	Polyuria, polydipsia, blurry vision, and weight loss	HbA1c 9.4% (5.4% 6 mo ago). Anti-GAD, IA-2, ZnT8 Ab positive.	Treated with insulin. Was able to stay off insulin for 2 mo, but then placed back on it.

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Table (*continued*)

Author and country of publication	Demographic information	mRNA vaccine(s)	Timeline	Presentation	Workup	Clinical course/follow-up
No evidence of autoimmunity						
Sakurai et al[7] (2022) Japan	36 y/F Asian	Pfizer-BioNTech (1 dose)	3 d after vaccine	Polyuria, polydipsia, fatigue followed by DKA 7 d later.	HbA1c 7%. C-peptide low. Negative Ab testing.	Discharged on insulin. No follow-up information.
Sato et al[14] (2022)[a] Japan	43 y/M Asian	mRNA based vaccine (2 doses)	2 d after second dose	Polyuria, polydipsia, and weight loss followed by DKA 10 d later.	HbA1c 8% (5.6% 1 mo ago). Fasting C-peptide low. Negative Ab testing.	Discharged on long-term insulin. Similar requirements at 5-mo follow-up.
Sasaki et al[15] (2022) Japan	45 y/F Asian	Pfizer-BioNTech (1 dose)	8 d after vaccine	DKA	HbA1c 7.2% Negative Ab testing.	Discharged on insulin. No follow-up information.
Makiguchi et al[17] (2022) Japan	65 y/F Asian	Pfizer-BioNTech (2 doses)	Few days after second dose	DKA	HbA1c 9.4%. C-peptide normal. Negative Ab testing.	Discharged on insulin. No follow-up information.
Ohuchi et al[16] (2021)[a] Japan	45 y/M Asian	Pfizer-BioNTech (2 doses)	3 d after second dose	Polyuria, polydipsia, and weight loss	C-peptide low. Negative Ab testing.	No discharge/follow-up information.

Abbreviations: Ab = antibody; DKA = diabetic ketoacidosis; GAD = glutamic acid decarboxylase; IA-2 = insulinoma-associated protein 2; TPO = thyroid peroxidase.
[a] Both patients were also on nivolumab (every 4 weeks) for malignant melanoma for the past 1 year, with last dose being 10 days prior to symptom onset.

symptoms concerning for hyperglycemia or diabetic ketoacidosis, especially in the 4 months from recent COVID-19 vaccination. This should be accompanied by early testing for type 1 diabetes, including autoantibody evaluation and initiation of insulin if indicated. Additionally, the lack of literature on this topic must be addressed. There is a need for a centralized repository for collection of data related to autoimmune manifestations of COVID-19 vaccination, including but not limited to type 1 DM, so that well-designed studies can be conducted and mechanisms underlying the disease process can be elucidated.

Conclusion

New-onset type 1 DM has been reported after COVID-19 mRNA vaccination. Clinicians should maintain a high index of suspicion and pursue early testing for the same to reduce adverse outcomes and improve long-term prognosis. It must be noted that these adverse events are exceedingly rare and majority of individuals can be vaccinated without the risk of development of type 1 DM.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

Consent was obtained from the patient.

Author Contributions

A.H. designed the study; U.B. and A.H completed a review of literature; U.B., N.A., and R.B. wrote the initial draft which was edited by A.H.; all authors were involved in the interpretation of results. All authors reviewed and approved the final manuscript.

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