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ORIGINAL ARTICLE

Type 1 diabetes mellitus following SARS-CoV-2 mRNA vaccination

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Abstract

Purpose Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines have been reported to trigger immune side effects. Type 1 diabetes as a manifestation of autoimmune/inflammatory syndrome induced by adjuvants has been reported in a limited number of cases after vaccinations. A few type 1 diabetes cases after SARS-CoV-2 vaccination have been reported. This study aims to report type 1 diabetes cases associated with the mRNA-based SARS-CoV-2 vaccination.

Methods We report four cases of type 1 diabetes mellitus after mRNA-based SARS-CoV-2 vaccine, BNT162b2 (Pfizer–BioNTech). In the medical history, one subject had autoimmune thyroid disease. All patients had autoantibodies against glutamate decarboxylase.

Results In the presented case series, type 1 diabetes developed a few weeks after BNT162b2 vaccination. After developing type 1 diabetes, the insulin dose requirements of all patients decreased rapidly, and the need for insulin therapy in three patients disappeared during follow-up. Acute deterioration of glucose regulation in a patient followed by BNT162b2 administration may be due to vaccine-induced autoimmune diabetes.

Conclusion Vaccination with BNT162b2 may trigger type 1 diabetes.

Keywords SARS-Cov-2 mRNA vaccination · Type 1 diabetes mellitus · Autoimmunity · Glutamate decarboxylase · Spike Protein

Introduction

During the Coronavirus Disease-19 (COVID-19) pandemic, reducing the hospitalization and mortality rate due to the disease with effective vaccination has been the most crucial issue. The two messenger RNA (mRNA) based Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines, the BNT162b2 (Pfizer-BioNTech) and the mRNA 1273 (Moderna) were developed in a short time. These mRNA-based vaccines are highly effective in preventing symptomatic COVID-19 [1, 2].

While vaccination against SARS-CoV-2 is ongoing worldwide, the mRNA-based SARS-CoV-2 vaccines have been reported to trigger immune side effects by adjuvants [3–8]. The autoimmune/inflammatory syndrome induced by adjuvants (ASIA), first proposed by Shoenfeld and Agmon-Levin in 2011, defines a disease entity encompassing a broad spectrum of autoimmune/inflammatory conditions with heterogeneous severity [9]. Subacute thyroiditis, Hashimoto's thyroiditis, adrenal gland insufficiency, primary ovarian insufficiency, and type 1 Diabetes Mellitus have previously been reported as endocrine manifestations of ASIA [10]. After hepatitis B and human papillomavirus vaccinations, a few type 1 Diabetes Mellitus cases have been reported in the literature [11]. Data on the possible association between SARS-CoV-2 vaccination and the development of type 1 diabetes are very limited [6, 12–14].

Therefore, we present a series of four cases diagnosed with type 1 Diabetes Mellitus after BNT162b2 vaccination.

Materials and methods

A total of four cases is presented here. All patients were diagnosed and followed at Ankara Güven Hospital. Their

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Table 1 Clinical features and baseline laboratory results of the cases

	Case 1	Case 2	Case 3	Case 4
Age (years)	56	48	27	36
Gender	Male	Male	Female	Male
FPG (mg/dL)	440	352	320	526
HbA1c (%)	8.2	10.1	12.5	12.6
C-peptide (ng/mL)	1.5	0.97	0.87	0.38
GAD65Ab (IU/mL)	>2000	94	725	234
Time from vaccination to symptom onset (weeks)	2[a]	8	3	3

FPG fasting plasma glucose (normal range: 70–100 mg/dL), *HbA1c* glycated hemoglobin (normal range: 4.0–5.6%). C-peptide normal range 1.1–4.4 ng/mL. *GAD65Ab* glutamate decarboxylase antibody-65 (normal range: 0–10 IU/mL)

[a]After administration of second dose

clinical features and baseline laboratory results are summarized in Table 1.

Serum samples were analyzed for glutamic acid decarboxylase 65 antibody (GAD65ab) with the enzyme-linked immunosorbent assay (ELISA) method (EUROIMMUN AG, Germany). The sensitivity and specificity of the assay were 82% and 99% respectively (Islet autoantibody standardization program, 2015).

Case presentations

Case 1

A 56-year-old male was admitted to the outpatient clinic with significant weight loss, dry mouth, polyuria, and polydipsia. He had a medical history of vitiligo and Hashimoto's thyroiditis. He received the first dose of BNT162b2 in March 2021 and the second in May 2021. Fifteen days after the second dose of the vaccine, he had fatigue, dry mouth, and polyuria, and he lost 5 kg in a week. Six months earlier, his fasting plasma glucose (FPG) and glycated hemoglobin levels were 97 mg/dL and 5.9%, respectively. On physical examination, his body mass index (BMI) was 27.4 kg/m^2, and his waist circumference (WC) was 89 cm. At laboratory investigations, his FPG and HbA1C levels were high. He had ketonuria but not acidosis in the blood gas testing. Levels of fasting insulin and C-peptide was at the lower limit of the normal range. GAD65Ab was positive at high titers. His laboratory results are summarized in Table 1. Basal-bolus insulin therapy was started after euglycemia was achieved with intravenous insulin infusion therapy.

During three months follow-up period, his insulin requirement decreased gradually, and the patient discontinued insulin treatment due to frequent hypoglycemic events. After discontinuation of insulin treatment at the 3rd-month visit, his FPG, HbA1c, and C-peptide levels were 107 mg/dL, 6.5%, and 1.8 ng/mL, respectively.

Case 2

A 48-year-old patient was admitted to the outpatient clinic because of fatigue and hyperglycemia. He did not have personal or family history of autoimmunity or diabetes mellitus. Three months earlier, his fasting plasma glucose and HbA1c were 87 mg/dL and 5.6%, respectively, during his check-ups. Two months after the second dose of the BNT162b2 vaccine, hyperglycemia was found in his laboratory examination (Table 1) when he applied due to fatigue. His BMI was 21.9 kg/m^2, and his WC was 81 cm on physical examination. Laboratory examination revealed high FPG and HbA1c, and positive GAD65Ab (Table 1). The patient refused to initiate insulin treatment but received medical nutrition therapy. A low-carbohydrate diet was demonstrating frequent hypoglycemic events in continuous glucose monitoring.

Case 3

A 27-year-old female was admitted to the outpatient clinic with blurred vision, polyuria, polydipsia, weight loss, and vaginal candidiasis. She had no personal or family history of autoimmune diseases. Her physical examination was unremarkable. She received the first dose of the BNT162b2 vaccine in May 2021 and the second in July 2021. She developed symptoms about three weeks after the second vaccination. On physical examination, BMI was 20 kg/m^2, and WC was 64 cm. Laboratory investigations revealed high HbA1c, FPG, low C-peptide, and positive GAD65Ab (Table 1). She received medical nutrition therapy and a basal-bolus insulin regimen. Her insulin requirements were gradually reduced, and she discontinued insulin treatment.

Case 4

A 36-year-old male was admitted to the emergency clinic with fatigue, dizziness, unintentional weight loss, and dry mouth on October 20, 2021. He had no personal or family history of autoimmune disease. The patient declared that he lost 10 kg within 15 days. He received two doses of CoronaVac® (Sinovac Life Sciences, Beijing) in April and May 2021, then two doses of the BNT162b2 on August 5 and September 27, 2021. On physical examination, his BMI and WC were 22.8 kg/m^{2,} and 98 cm, respectively. His mucous membranes were dry, and skin turgor was decreased. The random plasma glucose level was 656 mg/dL, and the venous blood gas study showed metabolic acidosis with a high anion gap (Ph:7.20 and HCO3:10.2 mEq/L). Ketone bodies in his urine test were three positives. Intravenous

insulin infusion and hydration were administered. A basal-bolus insulin regimen was applied once the blood glucose was lower than 200 mg/dL and ketoacidosis resolved. Laboratory investigations revealed low C–peptide, and high GAD65Ab levels (Table 1).

At the second-month follow-up visit, basal-bolus insulin therapy was reduced to 10 IU basal insulin.

Discussion

Phase III study of BNT162b2 demonstrated that a two-dose regimen conferred 95% protection against virus and had a similar incidence of severe adverse reactions to placebo [2]. After approval of the vaccines for emergency use against SARS-CoV-2, several autoimmune/inflammatory diseases associated with an inactivated whole virus and mRNA-based vaccines have been reported worldwide [3, 7, 8, 15, 16]. Type 1 diabetes mellitus related to vaccination against other viruses has rarely been reported as a phenomenon of ASIA in the literature (5). Additionally, a limited number of type 1 diabetes mellitus cases were reported after mRNA-based SARS-CoV-2 vaccines [11–14]. Herein, we report a case series of four newly diagnosed type 1 diabetes patients, possibly related to SARS-CoV-2 mRNA vaccination.

The spike protein of SARS-CoV-2 interacts with host cells through Angiotensin-I converting enzyme-2 (ACE-2) receptors [17]. Widespread expression of ACE-2 receptors in human tissues causes multiorgan involvement of COVID-19 [18]. Expression of ACE-2 was demonstrated in preferentially insulin-producing beta cells of islets and microvasculature pericytes in the pancreas [19]. Previously, SARS-CoV was suggested to cause diabetes by entering pancreatic islet cells and damaging them via ACE-2 receptors [20]. During COVID-19 pandemic, worsening of hyperglycemia, precipitation of ketosis, and ketoacidosis have been reported in diabetic patients [21, 22]. A multicenter study reported a remarkable increase in new-onset type 1 diabetes frequency among children infected by or exposed to SARS-CoV-2 [23]. Accumulating data suggested that SARS-CoV-2 may potentiate or aggravate type 1 and type 2 diabetes in infected individuals [22]. Epidemiological and mechanistic studies were recommended to ascertain the autoimmunity in beta cells of the pancreas induced by SARS-CoV-2 [19, 23, 24]. However, further studies did not confirm the enriched expression of ACE–2 in islet cells [25, 26]. Therefore, it is not yet possible to certain of a causal relationship between SARS-CoV-2 and new-onset diabetes.

The adjuvants in vaccines strengthen and extend the time of the immune responses. They are usually safe but may influence innate and adaptive immune systems via activation of B lymphocytes, alterations in immunological balance, and molecular mimicry and may activate the autoimmune response in genetically susceptible subjects [10, 27]. The endocrine system was reported as a target of ASIA syndrome caused by adjuvants of HPV, HBV, and influenza vaccines [11, 28, 29]. Subacute thyroiditis was the most reported autoimmune/inflammatory phenomenon after vaccination [4, 5], while type 1 diabetes mellitus was rarely reported as a manifestation of ASIA caused by vaccines [11]. In the study of Vojdani et al., cross-reactive interactions between the SARS-CoV-2 proteins and self–antigens of the host were explored as a possible link between autoimmunity and COVID-19 and vaccination against SARS-CoV-2 [30]. They demonstrated that monoclonal anti-SARS-CoV-2 spike protein and nucleoprotein antibodies cross-react with the human target proteins, including GAD65, related to most autoimmune diseases [30]. Therefore, molecular mimicry between the SARS-CoV-2 antigens and the human target proteins may be one of the possible underlying mechanisms of the SARS-CoV-2 vaccine-induced islet autoimmunity.

To date, thirteen cases of type 1 diabetes mellitus with vaccines other than against SARS-CoV-2 have been reported in the literature; however, no information was available regarding the time from the exposure, clinical and demographical features of the cases [11]. The BNT162b2 mRNA vaccine does not contain classical adjuvants [31]. Instead, self-adjuvant features of "mRNA", and polyethylene glycol lipid conjugates that act as adjuvants in mRNA-based SARS-CoV-2 vaccines were suggested to trigger autoimmune reactions [3, 32]. The first reported case of type 1 diabetes after the mRNA-based SARS-CoV-2 vaccine had concomitant Graves' disease and preexisting type 2 diabetes [6]. In addition, newly developed type 1 diabetes mellitus after mRNA-based SARS-CoV-2 vaccine was reported in three patients [12–14]. Table 2 summarizes the case reports of new-onset type 1 diabetes after the SARS-CoV-2 vaccine. Among our cases, the time from vaccinations to the disease onset was two to eight weeks. Three patients entered the honeymoon period with a rapid decrease in the need for insulin therapy shortly after diagnosis. Racial differences may be one of the reasons for the difference in insulin dose requirements between previously reported cases and the recent ones. Three of the cases were presented after the second dose of BNT162B. One case was presented days after the first dose of BNT162B. High titers of GAD65Ab supported the diagnosis of autoimmune diabetes in all cases.

In our series, the insulin dose requirements of all patients decreased rapidly, and the need for insulin therapy in three patients disappeared during follow-up. A "remission phase" otherwise named as "honeymoon period" may occur during the process of type 1diabetes. The pathogenesis of this complete or partial remission has not been fully understood yet [33]. The most accepted mechanism is transient beta cell recovery induced by treatment of glucotoxicity with exogenous insulin [34]. Downregulation of immune response by providing of normoglycemia and changes in frequency of

Table 2 Review of case reports with new-onset type 1 diabetes after the mRNA-based SARS-CoV-2 vaccine

	Patrizio et al. [6]	Sasaki et al. [12]	Yano et al. [14]	Sasaki et al. [13]
Age (years)	52	73	51	45
Gender	Male	Female	Female	Female
SARS-Cov-2 vaccine	BNT162b2	mRNA 1273	mRNA 1273	BNT162b2
HbA1c (%)	8.2	9.3	10.3	7.2
FPG (mg/dL)	NA	318	648	344
C-peptide (ng/mL)	1.0	1.8	1.72	0.33
GAD65Ab (IU/mL)	61.2 IU/mL (0–1)	>2000	Negative	Negative
ICA	NA	Negative	Negative	Negative
Insulin autoantibody	NA	Positive	Positive	Negative
Time from vaccination to symptom onset	4 weeks[a]	8 weeks[a]	6 weeks[b]	3 days[b]

FPG fasting plasma glucose (normal range: 70–100 mg/dL). *HbA1c* glycated hemoglobin (normal range: 4.0–5.6%), C-peptide normal range: 1.1–4.4 ng/mL, GAD65Ab glutamate decarboxylase antibody-65 ICA: islet cell antibody, NA not available

[a]After administration of second dose

[b]After administration of first dose

several immune cells are the other proposed mechanisms for the remission phase [35, 36]. Previously, Kuchay et al. reported three patients with COVID-19-related acute-onset diabetes and diabetic ketoacidosis, whose need for insulin therapy diminished over 4–6 weeks and control with oral antidiabetics was possible in the follow-up. Authors hypothesized that a recovery phase in pancreatic β-cells developed after the alleviation of direct cytotoxic injury caused by SARS-CoV-2 infection [37]. Unlike their cases, islet autoantibodies were positive in our patients. Therefore, the pathogenesis of diabetes and the triggering of the remission phase may be different in present cases. There may be a mild and transient attack on pancreatic β cells induced by the SARS-CoV-2 vaccines through molecular mimicry. Another mechanism may be an exacerbation caused by the immune-stimulating effects of vaccines in individuals with an individual predisposition to autoimmunity. Long-term follow-up data on these cases and further studies are needed to understand the possible mechanisms of vaccine-induced diabetes.

In conclusion, we report a case series showing the development of type 1 diabetes following the SARS-CoV-2 vaccine. More data are needed to clarify the role of vaccines against SARS-CoV-2 and in developing type 1 diabetes and other autoimmune diseases. The vaccination program is the cornerstone of the fight against the worldwide COVID-19 pandemic. During this period, clinicians should be kept in mind that type 1 diabetes may occur as a rare phenomenon of ASIA syndrome, and new-onset cases should be evaluated from this perspective.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author contributions BİA, and UÜ performed the literature search and drafted the manuscript. All authors (BİA, UÜ, and MC) coordinated the patient's care; read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical statement Written informed consent forms were obtained from all cases.

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