Review Article

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Glycemic Adverse Effects of Sars-CoV-2 Vaccination

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Abstract

Background: *Several cases of diabetes were recently reported in individuals vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).*

Objective: *To determine characteristics and patterns of glycemic changes occurring after SARS-CoBV-2 vaccination.*

Methods: *Pubmed search up to May 9, 2022. Search terms are diabetes, hyperglycemia, SARS-Cov-2, vaccine, COVID-19, hyperglycemic crisis. Case reports, case series, pertinent in-vitro studies and review articles are included.*

Results: *In ambulatory patients with type 1 diabetes, COVID-19 vaccination may transiently worsen glycemic control as measured by continuous glucose monitoring (CGM). 5 cases of newly diagnosed immune-mediated type 1 diabetes were reported 7-28 days after administration of COVID-19 vaccines. 4 Japanese patients presented with fulminant type 1 diabetes 3-6 days after receiving COVID-19 vaccines. 10 patients with newly diagnosed type 2 diabetes presented with hyperglycemic crises 3-36 days post-vaccination. In 7 patients with pre-existing type 1 and type 2 diabetes, COVID-19 vaccine has triggered hyperglycemic crises 15 hours to 10 days post-vaccination. These glycemic adverse effects may occur following the first or second dose of various types of COVID-19 vaccines. The underlying mechanisms are unclear but are likely multifactorial. No specific subject or vaccine factors that might predispose to develop glycemic complications of COVID-19 vaccine could be identified.*

Conclusions: *The timing of onset of glycemic complications in relation to COVID-19 vaccine administration suggests a causal relationship. Physicians and vaccinated individuals with and without diabetes should be mindful of these uncommon glycemic adverse effects of COVID-19 vaccine.*

Keywords: diabetes, COVID-19 vaccine, glycemic control, HbA1c, hyperglycemic crisis.

Introduction

COVID-19 infection has been shown to worsen glycemic control, trigger hyperglycemic crisis, and possibly induce new-onset diabetes [1, 2]. After the widespread use of COVID-19 vaccination, there have been several case reports and case series that describe similar glycemic complications in close temporal relationship with different types of COVID-19 vaccines. These glycemic effects include a wide range of complications ranging from mild worsening of glycemic control to induction of hyperglycemic crises and new-onset type 1 and type 2 diabetes. The timing of occurrence of these glycemic events in relation to administration of COVID-19 vaccine suggests that COVID-19 vaccination may be causally related to such events. The main purpose of this article is to review the latest data on the link between COVID-19 vaccination and post-vaccination glycemic complications.

Effect of COVID-19 vaccination on glycemic control in outpatients with diabetes

Mishra et al described 3 patients with type 2 diabetes who exhibited mild elevation of their fasting blood glucose values (from 95-110 mg/dl to 150-186 mg/dl) and postprandial glucose levels (from 122-165 mg/dl to 150-186 mg/dl) 1-6 days after receiving COVID-19 vaccine (Covishield, Astra-Zeneca) [3]. Glucose values returned to baseline 15-30 days after vaccination [3]. Subsequently, 4 studies examined the effects of COVID-19 vaccines on glycemic control, mostly in patients with type 1 diabetes, using CGM technology with variable results (Table 1) [4-7]. Thus, 2 studies did not report significant ef-

fects of various types of COVID-19 vaccines on the time of glucose values in range (TIR) (70-180 mg/dl) [4, 5]. However, in the largest available study (n=97), Heald et al [7] showed significant decrease in mean percentage of TIR during the 7 days post-vaccination (52.2%) compared with the 7 days prior to vaccination (55.0%) (Table 1). In fact, 58% of their patients had reduction in TIR post-vaccination, with 10% having more than 20% reduction in TIR. No effect on variability of glucose values was demonstrated after vaccination [7]. The results did not change in subgroups of patients classified by age, gender, intercurrent illness, and types of COVID-19 vaccines used (Pfizer-BioNtech and AstraZeneca) [7]. Unfortunately, these authors, did not explore the possible relationship between vaccine adverse effects and glycemic control [7]. Meanwhile, Aberer et al showed that patients with type 1 diabetes spent significantly less TIR on days on which vaccine adverse effects occurred (e.g. fever, fatigue, injection site reaction) [6]. Taken together, the above studies conducted in the outpatient setting suggest that COVID-19 vaccination may worsen glycemic control for at least 7 days in a subset of patients with type 1 diabetes. Adverse effects of the COVID-19 vaccines (fever, myalgia, malaise, pain at injection site, etc.) could be one factor contributing to this hyperglycemia.

Table 1: Effects of COVID-19 vaccination on glycemic control in outpatients with diabetes

Reference/country	Patients' characteristics	Type of vaccines	Main objective	Results
1.Piccini et al [4] Italy	n=39, type 1 diabetes on insulin pump, mean age 18	Pfizer-BioNTech and Moderna	*TIR 14 days after vs 14 days before first and second vaccine dose	No significant effect of vaccine on TIR
2.D'Onofrio et al [5] Italy	n=35, type 1 diabetes	Pfizer-BioNTech (Comirnaty)	*TIR 3 days after vs 14 days before first and second vaccine dose	No significant difference of vaccine on TIR
3.Aberer et al [6] Austria	n=58 type 1 diabetes and n=16 type 2 diabetes	Pfizer-BioNTech (87%), Moderna (6%), AstraZeneca (7%)	Glycemic ranges 3 days after the first vaccine dose vs 2 days prior	Significant deterioration of glycemic control in patients with type 1 diabetes associated with vaccine side effects
4.Heald et al [7] UK	n= 97 patients with type 1 diabetes, 52% women, median age 44	Oxford/AstraZeneca (54%), Pfizer-BioNTech (46%)	TIR 7 days after vs 7 days before first vaccine dose	Significant decrease in mean percentage of TIR after vaccination (52.2% vs 55.0%, P<0.03)

*TIR: time in range 70-180 mg/dl
F: female, M: man

COVID-19 vaccine-induced new onset immune-mediated type 1 diabetes

Immune-mediated or auto-immune type 1 DM is characterized by positive one or more pancreatic islet autoimmune antibodies such as autoantibodies to islet cell, glutamic acid decarboxylase 65 (GAD-65), zinc transporter 8, and insulin [8]. 5 cases of newly diagnosed immune-mediated type 1 diabetes were reported 7-28 days after receiving first or second dose of several COVID-19 vaccines (mRNA based vaccine of Pfizer-BioNtech and Moderna or the adenovirus vector-based vaccine of AstraZeneca) (Table 2) [9-12]. One patient had history of autoimmune hypothyroidism and another had strong family history of autoimmune diseases [3]. Patients presented with severe hyperglycemia or DKA [10]. The case reported by Patrizio et al was unique because their 52 year-old-man converted from well-controlled type 2 diabetes to immune-mediated type 1 diabetes. In addition, he presented with another auto-immune disorder: Graves' disease (Table 2) [12].

Table 2: Cases of immune-mediated type 1 diabetes induced by COVID-19 vaccine

Reference/country	Patient's age/race/gender	Type of vaccine	Timing of onset of hyperglycemic symptoms after receiving the vaccine	Personal/Family history of autoimmune diseases	HbA1c value on admission
1.Bleve et al [9] Italy	57 y/o Caucasian F	Vaxzevria ChAdOx1-S (Astra-Zeneca)	7 days after first dose	First degree relatives with type 2 diabetes, Hashimoto's thyroiditis and vitiligo	10.4% (14 days after admission)
2.Bleve et al [9] Italy	61 y/o Caucasian F	Pfizer-BioNTech (Comirnaty)	"Few days" after second dose	Patient has autoimmune hypothyroidism	11.5% (1 month after vaccine)
3.Yano et al [10] Japan	51 y/o Japanese woman	Moderna mRNA-1273	28 days after first dose	Positive insulin antibodies, anti-thyroglobulin and anti-peroxidase antibodies	10.3%
4.Sasaki H et al [11] Japan	73 y/o Japanese F	Moderna mRNA-1273	7 weeks after second dose	Had history of mild untreated type 2 DM	9.3%
5.Patrizio et al [12] Italy	52 y/o man	Pfizer BioNTech	4 weeks after second dose of Pfizer-	Patient had fairly controlled type 2 diabetes (HbA1c 7.0% 3 months before admission). Patient also presented with new-onset Graves' disease	10.1%

COVID-19 vaccine-induced new onset fulminant type 1 diabetes

Fulminant type 1 diabetes is a subtype of type 1 diabetes first described by Imagawa et al [13] in Japan. It is characterized by drastic onset of DKA, marked hyperglycemia (blood glucose 800 mg/dl on average), irreversible degeneration of pancreatic β-cells, and near-normal HbA1c levels (<7.0% on average) [13, 14]. In addition, there is specific class II haplotype closely associated with this disease [14]. Islet-related anti-bodies are usually not detected in fulminant type 1 diabetes [13, 14]. Fulminant type 1 diabetes was initially reported in Japan and Korea. However, it was recently described in other areas of the world as adverse effect of the anti-cancer drugs: check-point inhibitors [15]. Four cases, all from Japan, of new-onset fulminant type 1 diabetes were reported 3-6 days after COVID-19 vaccination (Table 3) [16-19]. However, in the case described by Ohuchi et al [19], patient was also taking the check point inhibitor nivolumab known to rarely cause fulminant type 1 diabetes [15]. Interestingly, other vaccines have been shown to trigger fulminant type 1 diabetes. Yasuda et al [20] reported one case of 54-year-old Japanese man who developed fulminant type 1 diabetes 7 days after receiving influenza vaccine.

Table 3: Cases of fulminant type 1 diabetes induced by COVID-19 vaccine

Reference/country	Patient's age/race/gender	Type of vaccine	Timing of onset of hyperglycemic symptoms after receiving the vaccine	Personal/Family history of autoimmune diseases	Blood glucose on admission (mg/dl)	HbA1c value on admission
1.Sasaki K et al [16] Japan	45 y/o Japanese F	Pfizer-BioNTech	3 days after first dose	None reported	469	7.6%
2.Sakurai et al [17] Japan	36 y/o F	Pfizer-BioNTech	3 days after first dose	None reported	501	7.0%

3.Tang et al [18] Japan	50 y/o M (race not reported)	Inactivated CoronaVac	6 days after first dose	Father with type 2 diabetes	Not reported	"near normal'
4.Ohuchi et al [19] Japan	45 y/o M	Pfizer-BioNTech	3 days after second dose	Patient had malignant melanoma treated by nivolumab	655	Not reported
F: female, M: man						

COVID-19 vaccine-induced hyperglycemic crises in patients without history of diabetes

10 patients presented with hyperglycemic crises i.e. diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS), or a mixture of both, 3-36 days after receiving the first or second dose of COVID-19 vaccines (summarized in Table 4) [21-24]. These patients had clinical and biochemical profiles of type 2 diabetes. Thus, they were obese (body mass index 31.1-35.0 kg/m2) with absent islet antibodies and normal C-peptide levels. Because HbA1c values were not available right before vaccination, it cannot be excluded that these patients might have undiagnosed type 2 diabetes prior to vaccination. It should be emphasized that hyperglycemia of recent onset has the largest influence on raising HbA1c levels [25]. Thus, 50% of the HbA1c levels are determined by the plasma glucose levels in the preceding 1-month period [26]. Hence, these patients presenting with extremely elevated HbA1c values (12.0-17.1%) few weeks after COVID-19 vaccination could still have new onset type 2 diabetes. The course of type 2 diabetes triggered by COVID-19 vaccine appears to carry favorable prognosis. Indeed, hyperglycemia was controlled with metformin alone or metformin + dulaglutide few weeks after resolution of hyperglycemic crisis [22, 23].

Table 4: COVID-19 vaccine-induced hypertensive crises in patients with new-onset type 2 diabetes*

Reference/country	Patient's age/race/gender	Type of vaccine	Timing of onset of hyperglycemic symptoms after the receiving the vaccine	HbA1c value before admission	HbA1c value on admission
1.Edwards et al [21]/UK	59 y/o Latino M	ChAdOx1 nCoV-19 (AstraZeneca)	21 days after first dose	5.6%, 37 months prior	14.1%
2.Edwards et al [21]/UK	68 y/o White M	ChAdOx1 nCoV-19 (AstraZeneca)	36 days after first dose	6.5%, 24 months prior	14.7%
3.Edwards et al [21]/UK	53 y/o Black M	ChAdOx1 nCoV-19 (AstraZeneca)	20 days after first dose	6.2%, 18 months prior	17.1%
4.Abu-Rumailah et al [22] USA	58 y/o African M	Pfizer-BioNTech	Nocturia after first dose and worsening 2 days after second dose	Not reported	13.0%
5.Lee et al [23] USA	52 y/o F	Pfizer-BioNTech	3 days after first dose	6.2% in 2019	12.0%
6.Samuel et al [24] Switzerland	59 y/o M	ChAdOx1 nCoV-19 (AstraZeneca)	21 days after first dose	5.6%, 37 months prior	14.1%
7.Samuel et al [24] Switzerland	58 y/o M	Pfizer-BioNTech	6 days after second dose	Not reported, but blood glucose <120 mg/dl last 3 years	13.0%
8.Samuel et al [24] Switzerland	52 y/o F	Pfizer-BioNTech	3 days after first dose	6.2% 24 months prior	12.0%
9.Samuel et al [24] Switzerland	68 y/o M	ChAdOx1 nCoV-19 (AstraZeneca)	36 days after first dose	6.5% 24 months prior	14.7%
10.Samuel et al [24] Switzerland	53y/o M	ChAdOx1 nCoV-19 (AstraZeneca)	20 days after first dose	6.4% 18 months prior	17.1%
*It is possible that some of the above patients may have pre-existing undiagnosed type 2 diabetes (see text) F: female, M: man					

COVID-19 vaccine-induced hyperglycemic crises in patients with type 1 and type 2 diabetes

In patients with known diagnosis of type 1 and type 2 diabetes, COVID-19 vaccination may exacerbate diabetes control acutely and result in hyperglycemic crisis [23, 24, 27, 28]. Table 5 summarizes data from 7 patients (3 patients with type 1 and 4 with type 2 diabetes) who developed hyperglycemic crises 15 hours to 10 days after receiving the first or second doses of COVID-19 vaccines [23, 24, 27, 28]. Interestingly, the 2 patients reported by Lee et al had well-controlled type 2 diabetes (their HbA1c levels were 7.0 and 7.5%) and had previous COVID-19 infection approximately 1 year earlier. After resolution of hyperglycemic crisis, diabetes control was achieved by metformin alone in all 4 patients with type 2 diabetes [23, 24].

Table 5: COVID-19 vaccine-induced hyperglycemic crises in patients with pre-existing type 1 and type 2 diabetes

Reference/country	Patient age/ gender/type of diabetes	Type of vaccine	Timing of presentation after vaccination	HbA1c on admission	Comment
1.Ganakumar et al [27] India	20 y/o M, type 1	ChAdOx1 nCoV-19 (AstraZeneca)	3 days after second dose	14.1%	
2.Ganakumar et al [27] India	25 y/o F, type 1	COVAXIN (BBV152-inactivated whole virion)	6 days after second dose	16.3%	
3.Zilbermint and Demidowich [28] USA	24 y/o F, type 1	mRNA-1273 Moderna, type 1	15 hours	12.0%	Required 220 units intravenous insulin first 24 h
4.Lee et al [23] USA	59 y/o M, type 2	mRNA-1273 Moderna	2 days after first dose	13.2 %.	Had COVID-19 infection 10 months prior.
5.Lee et al [23] USA	87 y/o M, type 2	mRNA-1273 Moderna	2 days after first dose	Not reported	Had COVID-19 infection 1 year prior
6.Samuel et al [24] Switzerland	59 y/o M, type 2	mRNA-1273 Moderna	2 days after first dose	13.2%	Diabetes controlled by metformin after few weeks
7.Samuel et al [24] Switzerland	87 y/o M, type 2	mRNA-1273 Moderna	10 days after first dose	Not reported	Diabetes controlled by metformin after few weeks

F: female, M: man

Mechanisms of COVID-19 vaccine induced diabetes

The mechanisms underlying COVID-19 vaccine-induced new-onset diabetes or worsening of pre-existing diabetes are not fully understood. They are likely multifactorial and take place in a small subgroup of predisposed subjects. One possibility is that inflammatory and/or immunological response to the vaccine may result in acute stress and release of anti-insulin hormones (cortisol, catecholamines, growth hormone) precipitating hyperglycemic crisis [29]. Moreover, common adverse effects of COVID-19 vaccines such as malaise, mild fever, and myalgia may be contributing stressful factors. In addition, some authors propose the molecular mimicry or cross-reactivity theory and the autoimmune/Inflammatory syndrome induced by adjuvants (ASIA). Molecular mimicry refers to a close similarity between certain pathogenic elements contained in the vaccine and specific human proteins [30]. It follows that cross-reactivity may occur when amino acid homology exists between the pathogen and a given self-tissue protein. Thus, antibodies developed against the spike protein of SARS-CoV-2 following COVID-19 vaccination might cross react with human pancreatic tissues to trigger an autoimmune disorder such as type 1 diabetes in susceptible individuals. In fact, Vojdani et al [31] have shown that anti-spike antibodies of SARS-CoV-2 react strongly with the GAD-65, one of the major antigens involved in immune-mediated type 1 diabetes [8]. The ASIA theory entails development of an autoimmune disease due to the use of adjuvants in the vaccine. Adjuvants are immunological molecules that potentiate imunogenecity response of a vaccine [32]. However, in predisposed subjects, adjuvants may trigger autoimmune diseases [33]. Acute pancreatitis could be another potential mechanism by causing damage of pancreatic β-cells. Several cases of acute pancreatitis were reported shortly after COVID-19 vaccines [34-37]. However, all cases of COVID-19 vaccine-induced pancreatitis resolved after few weeks, and no hyperglycemia was recorded [34-37]. Furthermore, computed tomography of the pancreas performed in 2 patients who presented with fulminant type 1 diabetes after COVID-19 vaccination was unremarkable [17, 18].

Conclusions and current needs

Available data suggest that COVID-19 vaccines may induce new-onset type 1 and type 2 diabetes as well as temporary exacer-

bation of glycemic control in patients with prevalent diabetes ranging from mild hyperglycemia to hyperglycemic crises. Although the incidence of these complications is most likely underreported, it may be still considered uncommon given the large number of people who received COVID-19 vaccines worldwide so far. Unfortunately, the limited current data does not indicate any specific patient predisposing factors or vaccine type that may increase the risk of vaccine-induced diabetes or worsening hyperglycemia. Physicians should be aware of this uncommon adverse effect of COVID-19 vaccines. In addition, patients with diabetes should be counselled about the possibility of deterioration of glycemic control post-vaccination and asked to monitor their blood glucose values closely for several weeks after receiving first and second dose of COVID-19 vaccine. Equally important, physicians and nurses should inquire about prior COVID-19 vaccination in patients presenting with hyperglycemic crises or new onset diabetes. Cases suspected to be triggered by the vaccine should be reported to the Federal Drug Administration (FDA) and the manufacturer. No doubt, the benefits of vaccination against COVID-19 far outweigh its risks. However, every effort must be pursued to prevent and promptly treat the adverse effects of COVID-19 vaccines.

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