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COVID-19 Breakthrough Infections in Type 1 Diabetes Mellitus: A sub-study of the COVAD cohort

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COVID-19 Breakthrough Infections in Type 1 Diabetes Mellitus: A Substudy of the COVAD Cohort

Abstract

Objective:
To investigate the frequency, profile, and severity of COVID-19 breakthrough infections (BI) in patients with type I diabetes mellitus (T1DM) compared to healthy controls (HC) after vaccination.

Methods:
The second COVID-19 Vaccination in Autoimmune Diseases (COVAD-2) survey is a multinational cross-sectional electronic survey which has collected data on patients suffering from various autoimmune diseases including T1DM. We performed a subgroup analysis on this cohort to investigate COVID-19 BI characteristics in patients with T1DM. Logistic regression with propensity score matching analysis was performed.

Results:
A total of 9595 individuals were included in the analysis, with 100 patients having T1DM. Among the fully vaccinated cohort, 16 (16%) T1DM patients had one BI and 2 (2%) had two BIs. No morbidities or deaths were reported, except for one patient who required hospitalization with oxygen without admission to intensive care. The frequency, clinical features, and severity of BIs were not significantly different between T1DM patients and HCs after adjustment for confounding factors.

Conclusion:
Our study did not show any statistically significant differences in the frequency, symptoms, duration, or critical care requirements between T1DM and HCs after COVID-19 vaccination. Further research is needed to identify factors associated with inadequate vaccine response in patients with BIs, especially in patients with autoimmune diseases.

COVID-19 Breakthrough Infections in Type 1 Diabetes Mellitus: A Substudy of the COVAD Cohort

The ongoing COVID-19 pandemic has significantly impacted individuals living with autoimmune diseases worldwide. The development and widespread uptake of COVID-19 vaccines had been critical in containing and mitigating the impact of this virus. However, the emergence of COVID-19 breakthrough infections (BI), defined as the detection of SARS-CoV-2 or antigen in the respiratory samples of an individual ≥14 days after complete vaccination, has raised concerns about the effectiveness of vaccines.[1] A diagnosis of systemic autoimmune diseases (SAIDs) is likely to render individuals at a higher risk of severe BI.[2] Diabetic patients with poor glycaemic control are more susceptible to developing BIs due to associated cytokine dysregulation and premature immunosenescence (accelerated aging of the immune system) in hyperglycemia.[3] Additionally individuals with SAIDs such as T1 diabetes (T1DM) may be particularly predisposed due to hyperglycemia and consequent immune dysregulation.[4] Therefore it is imperative to understand the prevalence and risk factors for BI in adults with T1DM.

The COVID-19 Vaccination in Autoimmune Diseases (COVAD) survey was a self-reported online global survey that collected demographic information, clinical history, and details about COVID-19 vaccination in individuals diagnosed with autoimmune diseases (detailed methods as Supplementary File).[5,6] The COVAD dataset is a valuable resource that identified patient-reported outcomes including the risk factors for BIs and disease flares after COVID-19 infection in patients with various autoimmune disorders.[7,8] Medians and interquartile ranges (IQR) were used to summarize continuous data while frequencies and percentages were used to summarize categorical data. Chi-squared ($\chi 2$) and Mann-Whitney U tests were used to compare T1D patients to HCs for categorical and continuous variables, respectively. We conducted a subgroup analysis to explore the frequency, profile, and severity of BIs in patients with T1DM and compared these observations to healthy controls (HCs). BIs following COVID-19 vaccination can be multifactorial, so we performed a propensity score matching (PSM) analysis between the T1DM patients and HCs. Data was analyzed using IBM SPSS version 26 (IBM, Armonk, NY, USA).

Of 10,783 respondents at the time of data analysis, 733 unvaccinated and 324 single-dose respondents, and 131 incomplete responses were excluded. Out of the total 9595

individuals included in the final analysis 3435 were HCs and 100 patients had the diagnosis of T1DM (Table S1 in the Supplementary File). Among the HCs, 467 (13.5%) reported experiencing a BI once and 124 (3.6%) reported experiencing a BI twice. Among the 100 T1DM patients (66% female, 46% Caucasian), 16 (16%) experienced one BI, and 2 (2%) experienced BI twice (Table S2 in the Supplementary File). The median time to symptom resolution was 10 days (2.5 to 72 days) in T1DM patients who received 2 doses of vaccine and 14 days (6 to 18 days) in those who received 3 doses. The most prevalent symptoms during the first BI in T1DM patients were cough (62.5%), fatigue (50%), fever (37.5%), and myalgia (31.25%). Only one patient required hospitalization for supplemental oxygen requirement, however, did not require intensive care.

Supplementary Table S3 presents the population characteristics of T1DM before and after PSM analysis. The results of PSM analysis indicated that individuals with T1DM had no statistically significant increase in the risk of experiencing one-time BI [T1DM vs HC OR 1.2 (0.7-2.0), p= 0.490] or two-time BI [T1DM vs HC OR 0.5 (0.1-2.2), p= 0.399] as compared to HCs. (Table 1)

It has been hypothesized that diabetes-associated hyperglycemia impairs immune function and induces immunosenescence putting these patients at risk for BI even after full vaccination.[9] The PRO-VACS 2 study reported mild COVID-19 symptoms including cough, cold, sore throat, and fever in cases of BI in 24 fully immunized T1D patients.[10] The results are similar to the findings of mild COVID-19 BI symptoms in vaccinated T1DM patients. The above study also did not show any major effect of BI on glycaemic control in vaccinated patients. Another study by Basso et al. reported 2.41 times higher odds of contracting a BI in diabetics as compared to individuals without diabetes.[11] This contrasts with the findings of our study where there were no differences in the frequency of BIs between patients with T1DM and HC.s. A recent study by Jia et al. reported similar humoral antibody responses to SARS-CoV-2 mRNA vaccines during 12 months of follow-up as well as similar rates of BI in T1DM patients and HCs. [12]

Our study did not find significant differences in BI frequency, clinical features, or severity between T1DM patients and HCs, reaffirming comparable protection provided by vaccinations in both groups. Our study has some limitations that should be considered. The sample size of T1DM patients is relatively small, data on glycaemic control was not captured by the survey, and there is the possibility of inadvertent introduction of recall and selection

bias in the online survey. However, this study encompasses patient responses from a wide range of geographical areas. This anonymized, self-reported patient survey addresses the difference in perspective between patients and physicians about symptoms burden and vaccine side effects. Understanding the patient's perspective is imperative in addressing vaccine hesitancy. Further studies with larger sample sizes and longitudinal design may provide more definitive conclusions.

In conclusion, the results of our study suggest that vaccination against COVID-19 is as effective and safe in T1DM patients as compared to healthy controls. Type 1 diabetics should receive the full course of COVID-19 vaccinations to render immunity against the virus according to their local immunization policies. However, further research is required to identify factors associated with inadequate vaccine response in individuals with BIs, especially in patients with autoimmune diseases.

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Tables

Table 1: Comparison of clinical features and management strategies between type 1 diabetic patients and healthy controls after propensity score matching

	T1DM (n=14)	HC (n=14)	OR (95% CI)	p-value
Any symptoms	14 (100.0)	14 (100.0)		1.000
Fever	6 (42.9)	5 (35.7)		0.699
Fatigue	8 (57.1)	7 (50.0)		0.705
Muscle aches	5 (35.7)	9 (64.3)		0.131
Joint pains	3 (21.4	5 (35.7)		0.403
Cough	10 (71.4)	8 (57.1)		0.430
Difficulty breathing	2 (14.3)	5 (35.7)		0.190
Loss of smell	3 (21.4)	1 (7.1)		0.280
Loss of taste	3 (21.4)	2 (14.3)		0.622
Running nose	7 (50.0)	6 (42.9)		0.705
Congestion	5 (35.7)	7 (50.0)		0.445
Throat pain/scratchiness	5 (35.7)	9 (64.3)		0.131
Chest pain	0 (0)	1 (7.1)		0.309
Diarrhoea	5 (35.7)	4 (28.6)		0.686
Headache	4 (28.6)	9 (64.3)	0.2 (0.04-1.09)	0.058
Oral ulcers	2 (14.3)	3 (21.4)		0.622
Nausea/vomiting	0 (0)	0 (0)		-
Abdominal pain	1 (7.1)	3 (21.4)		0.280
Skin rashes	0 (0)	0 (0)		-
Hospitalisation	1 (7.1)	3 (21.4)		0.280
ICU care or other HDU	0 (0)	0 (0)		-
Oxygen requirement	0 (0)	1 (7.1)		0.309

Advanced treatment for COVID-19 infection	6 (42.9)	4 (28.6)		0.430

T1DM: type 1 diabetes mellitus, HC: healthy controls, OR: odds ratio, CI: confidence intervals, ICU: intensive care unit, HDU: high-dependency unit