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COVID-19 in Type 1 Diabetes Mellitus adult patients; effect of infection and vaccination

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ABSTRACT

Background: The impact of severe acute respiratory syndrome corona virus (SARS-CoV-2) infection on Type 1 Diabetes Mellitus (T1DM) patients and their humoral response against the virus infection or vaccination is presently unclear, as in extant research Type 1 and Type 2 DM is rarely distinguished. *Objective*: we aimed to investigate the impact of SARS-CoV-2 infection, any associated risk factors for hospitalization, and the COVID-19 IgG antibody levels in T1DM patients versus those obtained from healthy individuals. *Methods and subjects*: 58 T1DM patients and 56 healthy adults with documented COVID-19 diagnosis and/or documented vaccination were recruited from different clinics in Al-Karak Governmental Hospital to complete a questionnaire before collecting their serum samples for measuring IgG levels. *Results*: Our results revealed a statistically significant decrease in SARS-CoV-2 NP IgG antibody levels in COVID-19 infected T1DM patients compared to infected healthy individuals who served as controls, while, no significant difference was noticed in the levels of SARS-CoV-2 S1/S2 IgG antibody among vaccinated T1DM patients versus controls. After adjusting for associated risk factors, the risk of hospitalization due to COVID-19 for individuals with uncontrolled T1DM was significantly increased compared to controls, and among patients with T1DM, glycosylated hemoglobin (HbA1c) correlated negatively with the IgG levels. Moreover, IgG seropositivity was significantly associated with old age and smoking. *Conclusion:* Our findings point towards an increased need for vaccination for patients with T1DM, and suggest that glycemic control could be a vital measure for diminishing the impact of COVID-19 on these individuals.

Keywords: Covid-19, Type 1 diabetes mellitus, SARS-CoV-2 NP IgG, SARS-CoV-2, vaccination

1. INTRODUCTION

In December 2019, a new strain of virus causing severe acute respiratory syndrome was primarily detected in China, and was subsequently denoted as COVID-19 (Sun et al., 2020). The virus spread rapidly and, at the time of writing this article, more than 238 million cases had been reported worldwide (Sun et al., 2020). It is still unclear which factors influence COVID-19

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outcomes, but it appears that some comorbidities such as hypertension (HTN), diabetes mellitus type I, heart disease, obesity, tobacco use, and male sex are risk factors (Zhu et al., 2020).

Diabetes mellitus is a chronic metabolic condition manifesting as high levels of blood glucose. It affects around 422 million people globally, most of whom live in the countries of low and middle income (Schaffner et al., 2020). DM is directly responsible for 1.5 million fatalities per year. World Health Organization, (2016) reported that 13.1 percent of Jordanians are considered diabetics (Zhu et al., 2020). Although DM has been identified as one of the significant risk factors for developing severe forms of COVID-19 (Zhu et al., 2020), as most of these patients have type 2DM (T2DM) (Zmora et al., 2017), little is known regarding the role of T1DM in COVID-19 outcomes (Cariou et al., 2020). Although several authors have examined COVID-19 severity in T1DM patients, the analyzed samples were typically restricted to hospitalized patients (Wargny et al., 2020) or those referred to a registry (Ebekozien et al., 2020), or mortality was considered as the only outcome (Barron et al., 2020). As a result, more research is required to determine the SARS-CoV-2clinical outcomes in individuals with T1DM.

SARS-CoV-2 immunoglobulin G (IgG) (Zhao et al., 2020) and antibody (Abs) (Connolly et al., 2021) levels increase in severely ill COVID-19 patients during the acute as well as the recovery phase. Moreover, several studies that have been conducted before the pandemic of the COVID-19 have shown that defects in immunity are linked to hyperglycemia/insulin resistance in T2DM (Zhu et al., 2020), suggesting that metabolic diseases lessen vaccine effectiveness. People with autoimmune disorders (AD) (Zmora et al., 2017) are among the prioritized groups of patients who might benefit from COVID-19 immunization because of increased morbidity and mortality. Since these individuals were omitted from the clinical research that led to the licensure of these vaccinations, evidence on their effectiveness or adverse responses is presently lacking (Kim et al., 2021). However, more recent investigation suggests that a baseline function in the humoral immune response in people with AD following immunization is inconsistent. The first data on the response to mRNA vaccines in patients with various ADs was recently published, indicating that all patients had a response defined by the production of IgG Abs directed against SARS-CoV-2 protein S. In addition, in specific individuals with AD, a reduced humoral response to SARS-CoV-2 vaccination has been noted (Chiang et al., 2021).

More than 100,0000 cases and over 12,000 deaths have been confirmed in Jordan as of December 25th, 2021. In order to avoid further spread of the virus, BNT162b2 mRNA (BioNTech/Pfizer), ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), and BBIBP-CorV (Sinopharm) vaccines were acquired and were made available during COVID-19 immunization in the country. As only one study was conducted on the impact of lockdown measures on pediatric patients with T1DM in terms of complications, medication, and perceptions of the use of telemedicine (Odeh et al., 2020), little is known about COVID-19's impact on adults with T1DM, including factors that rise the hospitalization risk, seropositivity, and IgG levels after infection and/or vaccination.

To address this critical gap in extant knowledge, as a part of this study, the IgG antibodies among T1DM patients that have been infected by or were vaccinated against the SARS-CoV-2 virus were measured and were compared with those in non-diabetic control group. In addition, the IgG antibodies produced by different types of vaccines were compared while also determining the increase in the hospitalization risk due to COVID-19 among T1DM patients.

2. SUBJECTS AND METHODS

Study design and participants

This cross-sectional study was approved by the Ethics and Scientific Committees of the faculty of Medicine at Mutah University. The sample comprised of 58 T1DM adult patients (23 of whom received the diagnosis in the last 12 months), and 56 non-diabetic adults that served as controls. All participants had a documented COVID-19 diagnosis and/or vaccination and were recruited from different clinics at Al-Karak Hospital between September 2021 and January 2022.

After obtaining an informed consent from each participant, they completed a self-administered questionnaire that inquired into their age, sex, smoking, duration of diabetes, comorbid diseases, body mass index (BMI), time of COVID-19 infection or vaccination, and type of vaccine taken. Additional data was collected from medical charts, such as hemoglobin A1c (HbA1c) given as percentage, and any COVID-19 related hospitalization. After obtaining serum samples, for patients with prior SARA-CoV-2 infection, the Ichroma™—which is a COVID-19 IgG antibody test against virus Nucleocapsid Protein (NP) with clinical sensitivity and specificity of 95.8% and 97.0%, respectively—was used as a medical instrument for *in vitro* diagnosis (Trivedi et al., 2019).

A positive result was defined as an IgG level of 1.1 or more (Naiyar et al., 2021). As the coronavirus spike (S) protein serves as the immunogenin all approved vaccines (except Sinopharm which is based on inactivated virus) (Wang et al., 2020), antibody against S protein was used as a measure for humoral immunity elicited by these vaccines (Petrović et al., 2021; Wei et al., 2021). For this purpose, LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay against a recombinant spike protein (S1/S2) (DiaSorinS.p.A., Saluggia, Italy) was used according to the manufacturer's instructions. Results below 12.0 AU/ml were considered negative,

12.0–15.0 AU/ml borderline, and >15 AU/ml positive. All carried measurements were done by trained lab employees from a local medical equipment business, who took all necessary biosafety precautions. SARS-CoV-2 IgG output was expressed as arbitrary units (AU/ml).

Statistical analysis

The statistical software SPSS version 16 was used for data analysis where by frequency and percentage was calculated for qualitative variables. Student's t-test was used for the quantitative variables which were normally distributed; the chi-squared test was performed for categorical variables, with $p \leq 0.05$ indicating statistical significance. We conducted both univariate and multivariable stepwise logistic regression analysis with an inclusion criterion of $p<0.05$ to identify factors associated with SARS-CoV-2 seropositivity. We included all the predictors (age, gender, BMI, diabetes, overweight status/obesity, smoking, hypertension, duration of diabetes and HbA1c, time elapsed since COVID-19 infection or vaccination, and vaccine type). A separate analysis was performed to assess the associated factors with SARS-CoV-2 hospital admissions. For this analysis, time that lapsed since of COVID-19 infection or vaccination, and type of vaccine were removed and the results were expressed as an adjusted odd ratio (AdjOR). The significance level was set at $p <0.05$. The figures were generated using Rstudio.

3. RESULTS

The study involved 114participants (66.7% females / 33.3% males, mean age = 45.3 ± 13.4),58 of whom were T1DM patients (50.8%), and 56 were healthy controls (49.1%). Nearly 60% of participants were infected with COVID-19 and 88% of T1DM patients and 93% of controls were vaccinated. Pfizer vaccine was the most and Sinopharm was the least common vaccine in both groups. The average time that had lapsed since infection and vaccination was 12.5 months and about 5 months, respectively. IgG seronegative results were slightly higher in T1DM patients compared to controls. The demographic characteristics of groups as well as the COVID-19 and T1DM related items, are summarized in Table 1.

Table 1 represents the demographic characteristics, COVID-19 and T1DM related items of the participants, these include: the mean ± SD of participants' age, BMI, HbA1c, time since COVID-19 infection (mo) and since COVID-19 vaccination (mo) the percentages and the counts of participants' gender, smoking status, if they were HTN patients, time since diagnosis of T1DM, increase diabetic medication after COVID-19 Infection, previous COVID-19 infection, hospitalization due to COVID-19, COVID-19 vaccination status, COVID-19 Abs positivity, COVID-19 vaccine types.

Table 1 the demographic characteristics

Variables		T1DM group (N=58)		Controls (N=56)	
		Mean	SD	Mean	SD
Age		47.5	13.5	42.9	13
BMI		33.9	23.7	29.6	5.4
HbA1c		9.2	2.1	0.3	1.9
Time since COVID-19 infection (mo)		12	5.1	13.9	5.4
Time since COVID-19 vaccination (mo)		5.5	1.8	5	1.5
Variables		N	%	N	%
Gender	Male	23	39.7	15	26.8
	Female	35	60.3	41	73.2
Smoking status	Smoker	12	20.7	12	21.4
	Non-smoker	46	79.3	44	78.6
HTN	Yes	32	55.2	19	33.9
	No	26	44.8	37	66.1
Time since diagnosis of T1DM	≤ 12 mo	23	39.7	-	-
	≥ 12 mo	35	60.3	-	-
Increase diabetic medication after COVID-19 Infection	Increased	18	31	-	-
	Not affected	40	69	-	-
Hospitalization due to COVID-19	Yes	6	11.5	3	5.3
	No	52	88.5	53	94.7
Previous COVID-19 infection	Infected	35	60.3	33	58.9

	Uninfected	23	39.7	23	41.1
COVID-19 Vaccination status	Vaccinated	51	87.9	52	92.9
	Unvaccinated	7	12.1	4	7.1
COVID-19 Abs positivity	Missing	3	5.2	9	16.1
	Positive	48	82.8	45	80.3
	Negative	7	12	2	3.6
COVID-19 vaccine types used	Pfizer	30	52.6	24	42.9
	Sinopharm	22	38.6	24	42.9
	AstraZeneca	5	8.8	8	14.3

N: counts; %: percent; SD: Standard Deviation; T1DM: type 1 Diabetes Mellitus; BMI: Body Mass Index; mo: months; HTN: Hypertension.

The study findings indicate that previously COVID-19 infected T1DM patients had statistically significantly lower SARS-CoV-2 NP IgG antibody levels compared to healthy controls (54.2 ± 45.4 vs. 80.4± 34.9, p= 0.018). Moreover, vaccinated T1DM patients had lower SARS-CoV-2 S1/S2 IgG antibody levels compared to controls, which was not significant (60.3 ± 44.3 vs. 75.1±38.9, p = 0.09). Moreover, IgG antibody levels were nearly similar irrespective of the vaccine type used, as shown in Table 2.

Table 2 represents the Mean ± SD, 95% CI and the P-value of the SARS-CoV-2 NP IgG antibodies after infection and SARS-CoV-2 S1/S2 IgG antibodies after vaccination with variable vaccines

Variables		Mean ± SD	P-value	95% CI
SARS-CoV-2 NP IgG antibodies	T1DM	54.2 ± 45.4	0.018*	-53.5 - -12.0
	Normal	80.4± 34.9		
SARS-CoV-2 S1/S2 IgG antibodies	T1DM	60.3 ± 44.3	0.09	-44.1 - -9.2
	Normal	75.1± 38.9		
S1/S2 IgG antibodies after different types of COVID-19 Vaccines	Pfizer	42.5± 6.3	0.58	4.7 - 56.7
	Sinopharm	40.9± 6.8		
	AstraZeneca	48.3± 15.3		

*P < 0.05; Dependent Variable: COVID-19 IgG levels; T1DM: type 1 Diabetes Mellitus

Further, after adjusting for different associated factors mentioned earlier, having uncontrolled T1DM (measured by frequent hospital admissions due to diabetes) was a statistically significant risk factor for hospital admission due to COVID-19 complications, with an OR of 8.3 (95% CI = 1.2–59.1; p = 0.03). Age and smoking also emerged as significant predictors of IgG positivity, with the OR of 1.1 (95% CI = 1.02–1.2; p=0.014) and 0.2 (95% CI = 0.03–0.8; p=0.02), respectively (Table 3). Finally, the means of IgG levels for T1DM patient were negatively correlated with HbA1c (r = -0.234; p= 0.055), as shown in Figure 1.

Table 3 The associated factors with Hospital admission and IgG positivity due to COVID-19 using multiple logistic regression (MLR).

Variable	Adj. OR	95% IC	P-value
Likelihood of Hospital Admission due to COVID-19 infection			
Uncontrolled T1DM	8.3	1.2 – 59.1	0.034*
Likelihood of IgG positivity			
Age	1.1	1.02 – 1.2	0.014*
Smoking	0.2	0.03 – 0.8	0.02*

*P<0.05; 95% CI; Confidence Interval; Adj OR: Adjusted Odds Ratio; T1DM: type 1 Diabetes Mellitus.

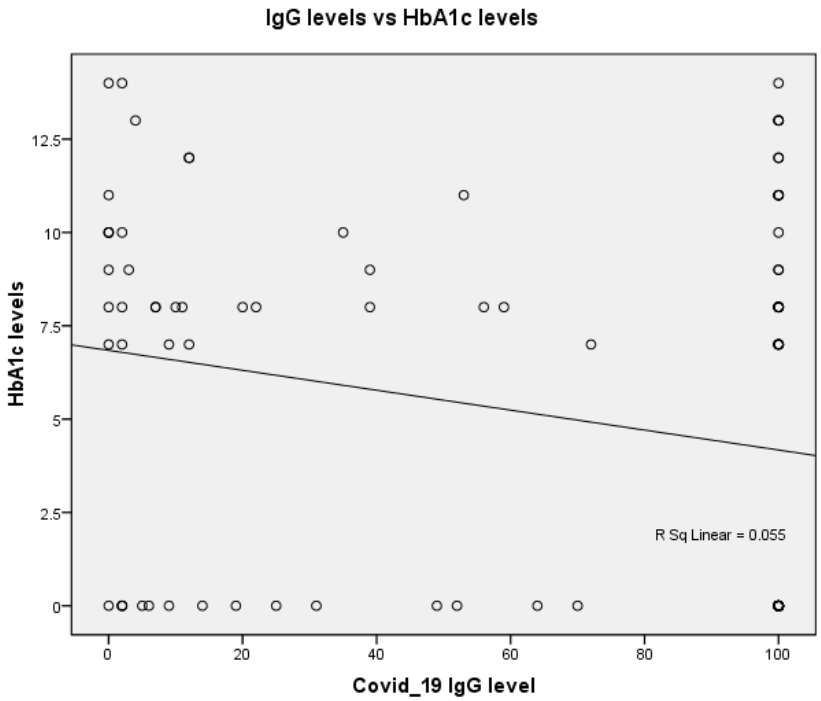

Figure 1 represents a scattered plot for the mean of SARS-CoV-2 NP IgG antibody levels and SARS-CoV-2 S1/S2 IgG antibody levels IgG serum levels versus HbA1c levels in T1DM patients; with R sq linear = 0.055.

4. DISCUSSION

Although the pathophysiological and virologic mechanisms behind the tangible link between diabetes and the risk of severe COVID-19 infection are presently unknown, patients with T1DM are more vulnerable to other respiratory viruses, such as the 2009 H1N1 virus (Adams et al., 2007). According to the available evidence, older T1DM patients are more likely to die from COVID-19 than are individuals that do not have diabetes (Wargny et al., 2020), while such link has not been established for those under the age of 21 (Cardona-Hernandez et al., 2021).

As T1DM is not universally recognized as the risk factor for adverse COVID-19 outcomes, people with T1DM were excluded in some countries from the high-risk categories given precedence during vaccination, but this was not the case for the UK. Furthermore, uncontrolled diabetes mellitus at the time of admission and during hospitalization may be the underlying cause of poor outcomes in COVID-19 patients (Holman et al., 2020) we compared COVID-19 severity among T1DM patients with that in the non-diabetic controls. After adjustment for age, BMI, presence of T1DM, uncontrolled T1DM, HbA1c levels, comorbid diseases such as hypertension, and other contributing risk factors, we found that the odds of COVID-19–related hospitalization increased among patients with uncontrolled T1DM. This result is in accordance with those obtained by Apicella et al., (2020), who showed that poor DM control would increase hospitalization rates among individuals with T1DM or T2DM. Moreover, the at-admission hyperglycemia among SARS-COV-2 patients was found to be an independent predictor for mortality (Yang et al., 2006). Following their study conducted in the UK on COVID-19 and T1DM, Holman noted a greater mortality risk in individuals with HbA1c >10% (Holman et al., 2020), while Barron indicated that those patients would suffer more from vascular DM-associated complications after the infection (Barron et al., 2020).

Knowing if T1DM patients have an attenuated humoral response to SARS-CoV-2 vaccination is crucial, as this finding has been reported in relation to AD (Connolly et al., 2021). Generally, several immunological defects are accompanied by hyperglycemia/insulin resistance. Diabetics have a significant decline in the immunological response to the vaccination against hepatitis B (Brinkløv et al., 2009), although results for influenza and varicella-zoster vaccinations have been less consistent, with overall responses to influenza immunization in T2DM patients being similar to controls (Smith and Poland, 2000). According to Seo et al., (2015), patients with and without DM had similar long-term Abs titers and Abs persistence for at least six months. Sauré et al., (2022) similarly noted that IgG seropositivity was considerably lower in persons with diabetes or chronic illnesses who received the Corona Vac vaccination.

In our study, IgG titer was performed 12 months and 5months after getting infection or vaccination, respectively, on average. Our results revealed that the levels of SARS-CoV-2 IgG are significantly lower in T1DM patients versus the controls and in those not vaccinated compared to vaccinated (the difference was more pronounced in DM patients). In our study, the seronegative results obtained for T1DM patients were comparable to those obtained for controls. The risk factors associated with seropositivity were examined using multiple logistic regression incorporating all predictors (age, gender, BMI, diabetes, overweight status/obesity, smoking, hypertension, duration of diabetes and HbA1c, time elapsed since COVID-19 infection or vaccination, and type of vaccine). Age and smoking were found to be negatively associated with IgG seropositivity, supporting previously obtained results (Bobrovitz et al., 2021; Weinberger and Grubeck-Loebenstein, 2012). This finding could be attributed to the decrease in T-cell-derived antibody production and B-lymphocyte generation with age. Moreover, antibody response against infectious agents and after vaccination may not be sufficient. Additionally, smoking was previously negatively associated with seropositive post-COVID-19 infection or immunization (Schaffner et al., 2020; Uysal et al., 2021).

The correlation between HbA1c and Abs levels in T2DM was previously studied (Pal and Banerjee, 2021), but such information on T1DM is lacking, while, Sheridan et al., (2012) reported the lack of correlation between HbA1c levels and antibodies in response to vaccination. Racine-Brzostek et al., (2021) noted significantly higher SARS-CoV-2 IgG levels in patients with HbA1c, and a weak positive correlation between the levels of both HbA1c and the antibodies was also noted. Our analyses suggest presence of a negative correlation between the levels of SARS-CoV-2 IgG and HbA1c. There is a bidirectional relationship between COVID-19 and DM as SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptors (Hamming et al., 2004), which are located in many metabolically active organs and tissues such as β cells of islets of Langerhans, adipose tissues, kidneys, and small intestine. As a result, SARS-CoV-2 may cause pleiotropic changes in glucose metabolism, complicating the pathophysiology of pre-existing diabetes or causing newly diagnosed diabetes. However, the classification of COVID-19 patients with newly diagnosed DM is difficult (Rubino et al., 2020) and there are no previous studies clearly assessing these individuals. As 23 of the 58 DM patients included in our study were diagnosed in the preceding 12 months, diabetic ketoacidosis (DKA) was the main complication of COVID-19 in those individuals (Verma et al., 2020; Shee et al., 2020). However, none of the patients in our study was admitted to the hospital because of DKA, and this could be attributed to their older age.

Significant limitations of this study warrant consideration. The data were collected from a single health system serving population from urban and suburban regions. Also, about half of the DM patients were diagnosed during the COVID-19 pandemic. The classification of COVID-19 patients with newly diagnosed diabetes is difficult because of termination of outpatient services in several healthcare facilities, including the routine care for diabetes mellitus that might lead to insufficient control of blood glucose at the time of lockdown (Verma et al., 2020). In uncontrolled (Verma et al., 2020), inefficient control of diabetes mellitus is related to severe disease and poor COVID-19 outcomes, as shown in our study. Moreover, many issues should be addressed here, such as the association between persistent and remnant glucose metabolism alterations and the severe COVID-19 infection. Further, among patients with preexisting diabetes, it is essential to ascertain if COVID-19 changes the basic pathophysiology and the history of the disease, answering these questions to inform the priority of the instant clinical attention, follow-up for continuous checking of the affected patients. Moreover, to assess the protective immunity, another assay of neutralizing antibody assays using different approaches should be used. Additionally, the limited number of participants did not give us the chance to conduct multivariate regression analyses focusing on theT1DM group.

The advice to be given to T1DM patients during Covid-19 pandemic is similar to that for the general population: use the masks, social distance instructions, avoid the unnecessary travel and the indoor gatherings. This is mainly essential as more-transmissible and possibly less vaccine-susceptible SARS-CoV-2 variants are circulating. Additionally, given the worse COVID-19 outcomes in people with lesser control of diabetes control, where, T1DM patients should adjust the glycemic control, targeting an HbA1c of <7%. Moreover, T1DM patients should be rapidly offered efficient vaccines, as our results showed a significant decrease in IgG levels in unvaccinated patients, as recent studies have demonstrated enhanced humoral response to third-dose SARS-CoV-2 vaccination in AD patients (Connolly et al., 2021).

5. CONCLUSION

Uncontrolled T1DM was accompanying the increased in the risk for adverse SARS-CoV-2 outcome (i.e., hospitalization), which might result from an impaired humoral response against SARS-CoV-2. Moreover, COVID-19 infected T1DM patients had a statistically significantly lowerSARS-CoV-2 NP IgG antibody levels compared to infected healthy individuals that served as controls, while, insignificant difference was noticed in SARS-CoV-2 S1/S2 IgG antibody levels among vaccinated T1DM patients versus the controls. In addition, old age and smoking were found to increase the seronegativity in both DM patients and controls.

These findings point towards increased need for vaccinating T1DM patients and suggest that the glycemic control improvement could be a vital measure for diminishing the risk of adverse COVID-19 outcomes.

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Ethical considerations

The study was approved by the Ethics Committee, Faculty of Medicine, Mu'tah University, Jordan (reference no. 302022).

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Informed Consent Statement

An informed consent was obtained from each subject enrolled in the study.

Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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