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Original Article

Antibody response following SARS-CoV-2 vaccination among patients with type 2 diabetes mellitus: A systematic review

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ABSTRACT

Background and aim: DM patients' antibody response after the COVID-19 vaccine is still unknown amid the COVID-19 vaccination rollout. This study aimed to explore the SARS-CoV-2 antibody response or seropositivity among DM patients following the COVID-19 vaccine administration.

Methods: We performed a systematic review of the literature consisting of observational or cross-sectional studies, which reported the antibody serology or seropositivity among DM patients by following the PRISMA 2020 guidelines.

Results: Eight studies with a total of 64468 patients were identified, and 5156 (7.9%) of them had diabetes. Most studies showed that antibody response and seropositivity in DM patients were lower than healthy population after one until four weeks following full COVID-19 vaccination dose.

Conclusion: The antibody response and seropositivity after the COVID-19 vaccine in DM patients were lower than in healthy subjects. Therefore, DM patients are expected to receive vaccines according to the dose and schedule appropriately and might be prioritized to receive vaccine boosters.

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1. Introduction

Up to November 12, 2021, The World Health Organization (WHO) has declared that coronavirus disease-19 (COVID-19) has affected more than 251 million people, and the global mortality rate has reached five million people [1]. Fortunately, the invention of COVID-19 vaccines throughout the world has enabled humans to battle the ongoing pandemic collectively. As of November 12, 2021, a total of more than seven million vaccine doses have been administered [1]. Moreover, vaccines played a crucial part in protecting vulnerable populations associated with increased risks of morbidity and mortality, including patients with diabetes [2].

Studies showed that the risk of mortality in COVID-19 patients was associated with various comorbidities, including hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), older age, obesity, and immunosuppression. COVID-19 patients with DM have an increased risk of morbidity and mortality due to innate and adaptive immune response alterations. In addition, a study by Pal et al. showed that COVID-19 patients with T2DM may not achieve seroconversion of SARS-CoV-2 antibodies, even after two weeks of diagnosis [3]. Therefore, primary prevention with vaccines remains the mainstay for mitigating the harmful risks associated with COVID-19 in patients with DM [2,3].

Regarding immune response in T2DM patients to vaccines, there is contrasting evidence on the matter. However, the antibody response after the COVID-19 vaccine among DM patients is still unknown amid this vaccination rollout. This is of particular concern given the increased risk of severe disease in the DM population.

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Therefore, this study systematically explored the SARS-CoV-2 antibody response or seropositivity among DM patients following the COVID-19 vaccine.

2. Material and methods

2.1. Systematic review

We performed a systematic review of the literature consisting of observational or cross-sectional studies, which reported the antibody serology or seropositivity among DM patients by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [4].

2.2. Information sources and search strategy

We performed a literature search through Pubmed and EMBASE databases. Keywords used were “COVID-19 vaccine” OR “COVID-19 vaccination” OR “SARS-CoV-2 vaccine” OR “SARS-CoV-2 vaccination” AND “Antibody” OR “Neutralizing antibody” OR “Anti-RBD” OR “Anti-S-RBD” OR “IgG” OR “Seropositivity” AND “diabetes mellitus” OR “DM” OR “diabetes” OR “diabetic” OR “T2DM”.

2.3. Inclusion and exclusion criteria

The inclusion criteria were patients aged >18 years old who received two doses of the COVID-19 vaccine, irrespective of the vaccine type. We excluded participants with particular

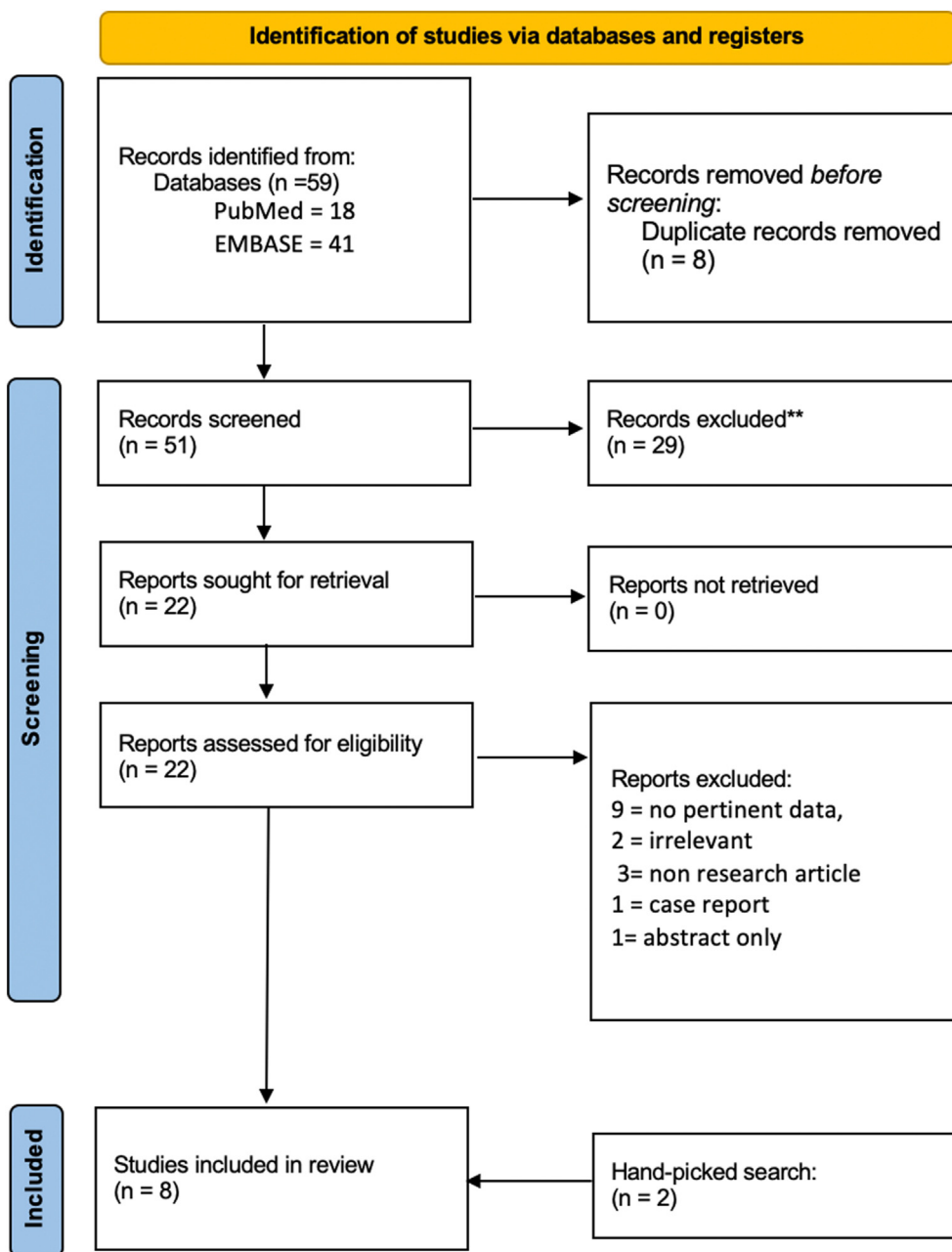


Fig. 1. Flowchart of the study.

comorbidities, such as pregnancy, autoimmune disease, chronic kidney disease, or underwent hemodialysis. We also excluded preprint articles, case reports, non-English articles, articles without pertinent data, non-research articles, and articles without full-text availability.

2.4. Study selection

Two independent reviewers (SL and NNM) screened the titles and abstracts for full-text eligibility and applied protocol inclusion and exclusion criteria to the full-text publication. Any discrepancies were discussed with third and fourth reviewers (HP and MRI). The study selection flow chart was shown in Fig. 1.

2.5. Data extraction

We collected the data regarding the first author name, country, study design, objective of the study, demographic characteristics, type of vaccine administered, the test used to check the antibody response, timing of the antibody testing, the antibody titres, and the seropositivity results.

2.6. Risk of bias

The risk of bias of included studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist (Table 3).

3. Results

After removing duplicate records, we identified 51 articles through the literature search and excluded 29 articles after titles and abstracts screening. We assessed the remaining 22 studies for eligibility. We also added two hand-picked literatures that related to this study but were not identified from the databases search. In total, we identified eight articles that reported the antibody serology or seropositivity rate after COVID-19 vaccination among DM patients (Fig. 1) [5–12].

3.1. Baseline characteristics

We included eight articles consisting of five observational studies, one case-control study, and two cross-sectional study.

Table 1
Characteristic of studies included.

No	First Author	Country	Study design	Objective of study	Population	Total patients	DM vs Non-DM patients	Mean Age (SD)
1	Nomura et al. [5]	Japan	observational study	Determine antibody (Ab) titres 3 months after the second dose of the BNT162b2 coronavirus disease-2019 (COVID-19) vaccine	Health-care worker	378	12 vs 353	43.9 (3.7)
2	Lustig et al. [6]	Israel	longitudinal cohort study	Assessed the early antibody responses and antibody kinetics after each vaccine dose in health-care workers	Health-care workers	2607	139 vs 2498	47.7 (9.5)
3	Watanabe et al. [7]	Italy	observational study	Explore variables associated with the serological response following COVID-19 mRNA vaccine.	Health-care workers	68	2 vs 66	29 (17)
4	Saure et al. [8]	Chile	surveillance study	Compare SARS-CoV-2 IgG positivity between vaccines using a dynamic national monitoring strategy	Chile population	59987	4626 vs NA	NA
5	Van Praet et al. [9]	Belgian	case control	Describe the dynamics of the humoral and cellular immune responses to the BNT162b2 mRNA Covid-19 Vaccine	COVID-19 naive nursing home residents	100	25 vs 75	85 (10)
6	Karamese et al. [10]	Turkey	cross sectional study	Determine the antibody responses after the 2 doses of inactivated SARS-CoV-2 vaccinations in people who were above 65 years old and to evaluate the factors affecting this response.	Turkey population	235	49 vs 186	70.38 (4.76)
7	Singh et al. [11]	India	cross sectional study	assessed the humoral immune response of both ChAdOx1-nCOV (Covishield™) and BBV-152 (Covaxin™) vaccines	Indian health care workers (HCW)	515	52 vs 463	44.82 (13.09)
8	Marfella et al. [12]	Italy	observational study	evaluate cell-mediated response to the COVID-19 vaccine with regard to diabetes status and glycaemic control.	Italian Population	578	251 vs 327	NA

There were 64468 patients, and 5156 (7.9%) of them had diabetes. Further details are provided in Table 1 [5–12].

3.2. Vaccination type and antibody testing

Five studies used the BNT162b2 vaccine (Pfizer/BioNTech) [5] [–] [7,9], one study used CoronaVac (Sinovac Life Sciences) vaccine [10], one study used both BNT162b2 and CoronaVac vaccines [8], and one study used both Covishield™ (ChAdOx1-nCOV) and Covaxin™ (BBV-152) vaccine [11]. Five studies reported the antibody titres quantitatively by using several kits, including Elecsys® Anti-SARS-CoV-2 assay, The SARS-CoV-2 IgG II Quant assay, LIAISON® S1/S2, and Anti-SARS-CoV-2 QuantiVac ELISA (IgG) test kit. Two studies reported the seropositivity of COVID-19 IgG/IgM. Most of the studies checked the response in 1–4 weeks following the second vaccine dose. Full descriptions of vaccines used in this study are provided in Table 2 [5–10].

3.3. Antibody titre or seropositivity

Among four studies that evaluated the antibodies quantitatively, only one study reported the antibody differences among DM and non-DM patients. Nomura et al. reported a lower antibody response in 12 DM patients in comparison with 353 non-DM patients (382 [211–741] vs 768 [436–1150]) [5]. Lustig et al. showed that only 27% (35/129) of DM patients had a positive IgG antibody response two weeks following the second vaccine dose [6]. Full descriptions of antibody response after vaccination in DM patients are shown in Table 2 [5–10].

4. Discussions

Immunogenicity has attracted increasing attention as an individual index for the efficacy of the SARS-CoV-2 vaccine [5]. It is depicted by observing the binding and neutralizing antibodies that developed after a full dose of vaccine, which might also be correlated with protection against SARS-CoV-2 [13]. In brief, the immune response after vaccination is developed by the innate and adaptive immune response. After the vaccine injection, lipid nanoparticles encapsulating mRNA (which encodes the SARS-CoV-2 spike (S) protein) and adenovirus (AdV) vectors gain entry into dendritic cells (DCs). Intrinsic adjuvant inside the vaccine triggered the

Table 2
Summary of antibody response among DM patients.

No	First Author	Type of vaccine	Test used to check antibody	Timing of test	Antibody titre (DM vs Non DM)	IgG Positivity (DM vs Non DM)	Description
1	Nomura et al. [5]	Pfizer/BioNTech BNT162b2 vaccine	Electrochemiluminescence immunoassay (ECLIA)	91 ± 15 days after the second inoculation	382 (211–741) vs 768 (436–1150)	NA	Diabetes mellitus is one of risk factors that is associated with lower Ab titre against SARS-CoV-2 Spike antigen 3 months after vaccination
2	Lustig et al. [6]	Pfizer/BioNTech BNT162b2 vaccine	IgG = for all study population, IgM, IgA, and neutralizing antibody = only in the enriched comorbidities subgroup. IgG = SARS-CoV-2 RBD-IgG assay (Beckman-Coulter, Brea, CA, USA) commercial test Igm IgA = IgM and IgA RBD-based ELISA	1–2 weeks after the first & second vaccine dose	NA	IgG: 35 VS 663 OR = 0.92 (0.39–2.19) IgA: 16 (8%) vs 308 (92%) vs OR = 0.30 (0.13–0.73)	The lower concentrations of IgG and lower detectable IgA antibodies observed in patients with diabetes suggest that DM patients have reduced antibody response following vaccination
3	Watanabe et al. [7]	Pfizer/BioNTech BNT162b2 vaccine	Elecsys® Anti-SARS-CoV-2 assay; Roche Diagnostics), which detects total antibodies against the SARS-CoV-2 spike (S) antigen in a sandwich electro-chemiluminescence assay	1–4 weeks after the second inoculation.	NA	NA	Diabetes is not associated with anti-SARS-CoV-2 antibody titre following vaccination (p = 0.876)
4	Saure et al. [8]	CoronaVac (Sinovac Life Sciences) and Pfizer/BioNTech BNT162b2 vaccine	COVID-19 IgG/IgM	4 weeks after first and second dose	NA	4 weeks after 1st dose Sinovac: 17.3% (11.3–23.4) pfizer: 40.5% (29.7–51.3%) 4 weeks after 2nd dose sinovac: 58.0% (54.4–61.6%) pfizer: 89.3 (85.5–93.2%) 8 weeks after 2nd dose sinovac: 60% (57–62.9%) pfizer: 92.5% (88.6–96.4%)	Diabetes was associated with reduced seropositivity among CoronaVac recipients
5	Van Praet et al. [9]	Pfizer/BioNTech BNT162b2 vaccine	Antibodies-RBD of S1 subunit of the spike (S) protein (IgG II Quant assay,	4, 8 and 24 weeks after the first vaccine dose	NA	NA	Diabetes was associated with a lower cellular response
6	Karamese et al. [10]	CoronaVac	Anti-SARS-CoV-2 QuantiVac ELISA (IgG) test kit	4 weeks from the first and second dose	NA	NA	The participants who had DM had lower antibody levels, and a significant difference was detected between the participants who had DM and who had not (Z = -4.524, p = 0.000) concerning mean antibody levels
7	Singh et al. [11]	Covishield™ (ChAdOx1-nCOV) and Covaxin™ (BBV-152)	LIAISON® S1/S2 quantitative antibody detection kit using indirect Chemiluminescence immunoassay (CLIA)	21–28 days after the 2nd dose	NA	Overall: 44/52 (84.6%) vs. 42/46 (91.3%) Covishield: 42/46 (91.3%) vs 375/379 (98.9%) Covaxin: 2/6 (33.3%) vs 70/84 (83.3%)	People with T2DM had a significantly lower seropositivity rate compared to those without in overall study participants, both in Covishield (p < 0.001) and Covaxin recipients (p = 0.003)
8	Marfella et al. [12]	Pfizer/BioNTech BNT162b2 vaccine	GenScript SARS-CoV-2 Surrogate Virus Neutralization	21 days after the 2nd dose	NA	NA	T2D patients with HbA1c >7% showed significantly reduced virus-neutralizing antibody capacity than normoglycaemic subjects and T2D patients with good glycaemic control (P < 0.05).

innate response and produced type I interferon and multiple pro-inflammatory cytokines. Thus, the activated DCs presented the antigen and co-stimulatory molecules to S protein-specific naïve T cells, which became activated and formed effector cells (cytotoxic T lymphocytes or helper T cells). Moreover, T helper (Th) cells helped S protein-specific B cells to differentiate into antibody-secreting plasma cells and promote the production of high-affinity anti-S protein antibodies. After vaccination, S protein-specific memory T cells and B cells develop and circulate along with high-affinity SARS-CoV-2 antibodies, which together help prevent subsequent

infection with SARS-CoV-2. All of these immune responses elicited by vaccination were required to neutralize the spike protein required for SARS-CoV-2 binding, fusion, and cell entry [14].

Previous studies showed that the immune response mentioned above might decrease in older and immunosuppressed persons, including those on certain immunosuppressive medications, post-solid organ transplants, and hematologic cancers [15]. There were several studies regarding antibody response after several types of vaccination among DM patients. DM patients were shown to mount an appropriate B-cell immune response after influenza and the 23-

Table 3
Risk of bias assessment using the Joanna Briggs Institute Critical Appraisal Checklist.

Author	1	2	3	4	5	6	7	8	9	10	11	Description
Nomura et al. [5]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Included
Lustig et al. [6]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included
Watanabe et al. [7]	Y	Y	Y	Y	Y	U	Y	Y	-	-	-	Included
Saure et al. [8]	Y	Y	Y	Y	Y	NA	Y	Y	-	-	-	Included
Van Praet et al. [9]	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	-	Included
Karamese et al. [10]	Y	Y	Y	Y	U	U	Y	Y	-	-	-	Included
Singh et al. [11]	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	Included
Marfella et al. [12]	Y	Y	Y	Y	Y	NA	NA	Y	Y	U	Y	Included

valent pneumococcal polysaccharide (PPV23) vaccination [16]. In contrast, adults with diabetes are stated to have a reduced response after Hepatitis B vaccination [17]. Therefore, these results provide an additional value that vaccine-preventable diseases ought to be given routinely in DM patients, considering that the DM patient population is susceptible to infection and its risk of deterioration.

DM patients infected with SARS-CoV-2 are known to be at risk of having a poorer prognosis, higher hospitalization rate, and higher mortality rate [18–21]. This occurs because of the alteration of the immune system that leads to an immunocompromised state. However, data regarding the immune response in DM patients with COVID-19 are still limited [16]. A study by Pal et al. in India showed that some T2DM patients with COVID-19 did not experience seroconversion even after two weeks of diagnosis. In this study, SARS-CoV-2 antibodies were not found in three out of the nine confirmed COVID-19 patients with T2DM [3].

This systematic review showed that the seroconversion rates after SARS-CoV-2 vaccination in T2DM patients were lower among the healthy controls. One study demonstrated a lower antibody titer quantitatively among DM patients after the SARS-CoV-2 vaccine [5]. However, DM was not correlated with lower Ab titres after age adjustment in this study. Karamese and his colleague also reported a significant difference in more inadequate antibody response among 49 DM patients older than 65 years old after being vaccinated with two doses of SARS-CoV-2 vaccine (CoronaVac) compared to the healthy control ($p = 0.000$) [10]. In addition to this, a prospective, multicentre cohort study, the Immune Response to COVID-19 Vaccination in People with Diabetes Mellitus (COVAC-DM) study demonstrated that age and estimated glomerular filtration rate were predictors for antibody levels after COVID-19 vaccination among type 1 and 2 diabetes, while HbA1c levels were not [22].

Nevertheless, it remains unclear whether this reduced response results from a delayed or a quantitatively lower immune reaction or is associated with poor clinical efficacy. The proposed hypotheses of this impaired response are the altered adaptive immune response among DM patients [17]. Patients with hyperglycaemia and insulin resistance had a reduction in the number of circulating helper T cells, the CD4⁺ to CD8⁺ lymphocyte ratio, lymphocyte proliferative response, impaired monocyte or macrophage, and defects with antigen presentation [12,23]. Hyperglycemia might also be responsible for the immune system weakness against SARS-CoV-2 vaccines due to virus-neutralizing antibodies and adaptive immune response (including T cells) dysfunction. The CAVEAT study observed that at 21 days after the first vaccine dose, neutralizing antibody titer and CD4 cytokine responses were lower in T2DM patients with HbA1c levels >7% than in patients with HbA1c levels ≤7%. Hyperglycemia at the time of vaccination might worsen the immunological response. Therefore, achieving adequate glycaemic control during the post-vaccination period improves the immunological response as stringent glycaemic control may predispose to a good immune response to the SARS-CoV-2 vaccine [12].

Of note, Sauré et al. compared the effectiveness of two SARS-CoV-2 vaccines that are widely available, Sinovac (the inactivated CoronaVac vaccine) and Pfizer–BioNTech's (the mRNA BNT162b2 vaccine), among the adult population in Chile. This study showed that after 16 weeks of the second dose, there was lower seropositivity among DM patients given the Sinovac vaccine than Pfizer–BioNTech's vaccine (47.1% vs. 94.0%). Strikingly, the seropositivity response in the DM group of this study was the lowest seropositivity response among other comorbidities in the population, including obesity, chronic pulmonary disease, chronic cardiovascular disease, and cancer [8]. In addition, a study by Singh et al. also showed that T2DM patients had a significantly lower seropositivity rate compared to those without, both in Covishield ($p < 0.001$) and Covaxin recipients ($p = 0.003$) [11].

In terms of neutralization antibody, the mRNA-1273 vaccine phase 3 clinical trial estimated that 68.5% (95% CI 58.5–78.4) of the protective effect of vaccination could be attributed to initial neutralization titers with some degree of protection occurring following vaccination, even when neutralization titers were not detected [24]. This might imply that while the magnitude of antibody response following vaccination is correlated with protection and the absence of antibody with risk, antibody test results only provide a partial picture of an individual's immune response, as there is no specific antibody test or antibody threshold that can determine an individual's risk of subsequent infection [15]. Meanwhile, although the seropositivity in the DM population seems lower, the antibody response was still robust and persisted. Therefore, patients with DM population should be prioritized to be vaccinated.

This study has some limitations. First, the total number of studies included was limited, as only several studies reported the antibody response after the SARS-CoV-2 vaccine among the DM population. Second, there was only one study that reported the quantitative serological response. Therefore, we could not analyze the mean total of antibody titers among DM patients after vaccination. Third, we could not analyze the confounding factors related to this study, including other comorbidities or age-related to any of these studies' results. Finally, concerning the reduced seropositivity as time passed by, we suggest that the DM population is a priority target group for a booster vaccination.

5. Conclusion

The seroconversion rates after SARS-CoV-2 vaccination in DM patients were lower than the healthy controls. However, the antibody response was still robust. Therefore, all DM patients are prioritized to get the SARS-CoV-2 vaccination on schedule as it is a higher risk of deterioration and poorer prognosis among COVID-19 patients with DM.

Ethics approval and consent to participate

Not Applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Declaration of competing interest

The authors declare that they have no competing interests.

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