

Heterogeneous immune response following SARS-CoV-2 vaccination irrespective of diabetes status in a group of subjects- a pilot study

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ABSTRACT

Objective

This study aims to assess the rate of COVID-19 infection and IgG seroprevalence of SARS-COV-2 among diabetic and non-diabetic subjects. This evaluation provides insight into how diabetic subjects respond to the COVID-19 pandemic, shedding light on the strength and duration of their immune responses following vaccination.

Materials and Methods

This cross-sectional study included 90 volunteers (45 DM and 45 NDM subjects) from BIHS General Hospital, who have received at least one dose of COVID-19 vaccine. SARS CoV-2 IgG antibody level was determined using ELISA. Data were analyzed using SPSS Version 26.

Results and Discussion

The SARS-CoV-2 IgG level was observed in both DM and NDM groups (14.48 ± 11.6 and 14.31 ± 11.45 BAU/mL) ($\text{BAU} \times 10^4$), with a gradual rise in antibody level by an increasing number of COVID-19 vaccine doses. No significant difference in respect to SARS-CoV-2 IgG antibody level was found between DM and NDM subjects ($p=0.949$). The rate of COVID-19 infection was found significantly higher in the non-diabetic group compared to the diabetic group ($p=0.001$). Among the BMI groups, a significantly higher level of IgG antibody was demonstrated among the obese population compared to normal and overweight groups ($p=0.037$).

Conclusions

Vaccination induced pronounced SARS-CoV-2 IgG response having no statistical difference in diabetic and non-diabetic groups. Heterogeneity in immune responses has been observed in both populations. The obese subjects had notably raised IgG levels. The incidence of COVID-19 infection was more higher in the nondiabetic compared to the diabetic group.

Keywords

COVID-19; diabetic, non-diabetic; COVID-19 vaccine; IgG level, heterogeneity.

INTRODUCTION

COVID-19 was first reported at the end of 2019 but developed into a pandemic by June 2020^{1,2}. In the beginning, chronic conditions like obesity, diabetes, and hypertension were attributed to incur a higher risk for COVID-19. Several reports demonstrated that the occurrence of COVID-19 was not only high among diabetics but also imparted greater severity and increased mortality^{3,4}. The SARS-CoV-2 virus is assumed to bind to ACE2 receptors that trigger pancreatic B cell depletion resulting in hyperglycemia⁵. That has prompted the necessity of careful management of COVID-19 patients with preexisting diabetic patients⁶.

Hosts' immune response has been reported to play a significant role in the pathogenesis of COVID-19⁷. The seroconversion of IgM and IgG antibodies was found to occur around 12 days post-symptom, with neutralizing antibodies arising within 14 to 20 days⁸. However, antibody

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titers showed a tendency to decrease after 60 days from the onset of symptoms⁹. It was observed that the IgG antibody titers decreased from 46.69 AU/mL on day 56, to 11.90 AU/ml on day 68 and became negative on day 80, suggesting that the antibodies to SARS-CoV-2 had waned over time¹⁰. In these circumstances, the vaccine is an effective and life-saving medical intervention¹¹. Intrinsic and extrinsic factors, however, are attributed to affecting immune responses following vaccination^{12,13}. Continuous monitoring of the seroprevalence of specific antibodies is regarded as an important measure in planning booster doses against the causative microbe, especially in vulnerable populations¹⁴. Taking advantage of developments in the field of molecular biology and biotechnology, scientists achieved the breakthrough in developing a vaccine against a new form of the virus by early September 2020¹⁵. With the approval of WHO, the distribution of vaccine commenced in late September 2021, and booster doses later in early 2022 to strengthen immunity¹⁶. The emergence of COVID-19 as a pandemic has taken the public health aback. It was assumed those with chronic conditions are not only at risk of contracting the disease but also subject to ranging forms of morbidity and mortality. Different professional bodies came up with precautionary measures for treatment modalities¹⁷. Patients with diabetes and hypertension showed exemplary adherence to the recommended measures¹⁸⁻²⁰.

This study aimed to determine the IgG seroprevalence of SARS-COV-2 among diabetic and non-diabetic subjects. This evaluation provides insight into how subjects with diabetes respond to the COVID-19 pandemic, helping us understand the strength and duration of their immune response.

MATERIALS AND METHODS

This cross-sectional study was conducted at BIHS General Hospital in Dhaka, Bangladesh. The study population included subjects aged between 20 and 70 years and those who had received varying doses of the COVID-19 vaccine. The diagnosis of Diabetes Mellitus was based on self-reporting. Obesity was determined according to body mass index (BMI), with those having a BMI < 23 kg/m² considered normal weight, those with a BMI between 23.1 and 24.9 kg/m² considered overweight, and those with a BMI ≥ 25 kg/m² considered obese. The eligible subjects provided socio-demographic information through interviews,

and five-milliliter blood samples were collected from each participant after obtaining informed consent.

An ELISA Kit (DRG ELISA Kit, EIA-6150, version 4.0, Marburg, Germany) was used to assess SARS-CoV-2 IgG antibodies targeting the Spike Protein S1's RBD. The assay procedures were performed according to the manufacturer's instructions. Serum samples were diluted 1:833, mixed, and 30 µL of the mixture was added to 470 µL of diluent. Absorbance at 450 nm (with a reference at 620 nm-630 nm) was read within 10 minutes. A result exceeding 50 BAU/mL was considered positive. Determination of IgG value for unknown samples was carried out by extrapolating the standard curve constructed using optical densities for the standards.

The Statistical Package for the Social Sciences (IBM SPSS, version 26) was employed for all statistical analyses conducted in the study. Additionally, Microsoft Excel 2010 was utilized for data editing and tabulation. Categorical variables were presented as frequencies and percentages (%), while quantitative variables were summarized using means and standard deviations (±SD). The influence of variables on the mean antibody titer was evaluated using Student's unpaired-'t' test, one-way ANOVA, and Chi-square test. The significance statistic was defined as p-value <0.05.

Ethical Clearance

This study was reviewed and approved by the Ethical Review Committee (ERC) of Bangladesh

University of Health Sciences (BUHS) (Memo no: BUHS/ERC/EA22/344). The participants provided voluntary consent to participate in this study.

RESULTS

Socio-demographic and clinical characteristics of the subjects

A total 90 subjects were enrolled in the study; of them 50% were non-diabetic and the rest were diabetic. The gender distribution of the study subjects male vs female (54% vs 46%) did not show any statistical difference (p=0.716). Mean (±SD) age of the study subjects was 42.34±13.30 (range: 20-70 years). Among the total subjects, 39 (43%) had COVID-19, rest 51 (57%) had no history of the infection. The majority of the subjects (81%) had received three doses of the COVID-19 vaccine, while 13% and 6% had two doses and one dose, respectively (Table 1).

Table 1: Characteristics of the study subjects

Variable	Number (%)
Gender	
Male	49 (54%)
Female	41 (46%)
BMI range groups (BMIGr) (Kg/m²)	
BMIGr1	33 (37%)
BMIGr2	25 (29%)
BMIGr3	32 (36%)
History of COVID-19 infection	
Yes	39 (43%)
No	51 (57%)
SARS-CoV-2 vaccination	
1 Dose	05 (6%)
2 Doses	12 (13%)
3 Doses	73 (81%)

Results were expressed as number (percentage)/mean \pm SD and range (Minimum-Maximum) as appropriate. A $p < 0.05$ was taken as the level of significance. BMIGr1, normal BMI (< 23); BMIGr2, overweight (23.1-24.9); and BMIGr3, obese (≥ 25).

COVID-19 infection of the study subjects: between diabetic vs non-diabetic

The distribution of subjects with a history of COVID-19 infection was summarized in Table 2. The number of diabetic subjects contracted COVID-19 was 11 (28%) against 28 (72%) non-diabetic group, which demonstrated a significant association ($p = 0.001$).

Table 2: History of COVID-19 infection among the diabetic vs non-diabetic subjects

COVID-19 Infection	Diabetic vs Non-diabetic		p value
	Diabetic	Non-Diabetic	
Yes (39)	11 (28%)	28 (72%)	0.001
No (51)	34 (67%)	17 (33%)	

Results were expressed as frequency (percentage). Statistical difference was calculated by using Chi-square. A $p < 0.05$ was taken as the level of significance.

SARS-CoV-2 IgG antibody status of the subjects

The mean (\pm SD) of SARS-CoV-2 IgG antibody level (BAU/mL) in all subjects was $13.28 \pm 9.35 \times 10^4$. In diabetic and non-diabetic subjects, the levels were 12.91 ± 8.58 vs. 13.65 ± 10.15 , which appeared to be almost similar ($p = 0.713$).

SARS-CoV-2 IgG level was looked into based on contracting COVID-19, vaccination, and obesity in diabetic and non-diabetic subjects, and months since the last vaccine dose (Figure 1). Distribution of IgG level was found concerned between 1 to 10 months in the diabetic group where 41 (97.8%) subjects and the non-diabetic group had IgG levels concentrated between 5-10 months (Fig A vs E). The diabetic subjects who contracted COVID-19 ($n = 11$) had their IgG levels distributed between 3 to 10 months, but their non-diabetic counterparts ($n = 28$) had IgG levels distributed mostly 82% (23 out of 28) between 7 to 10 months (Fig B vs F). Distribution of absolute IgG levels following 3rd dose vaccination in the diabetic group ($n = 41$) showed no particular pattern over 1 to 10 months. In the non-diabetic group, 84.4 % (27 out of 32) had IgG concentrated between 5 to 10 months (Fig C vs G). The IgG level among the diabetic obese ($n = 19$) group showed scattered distribution, suggesting a heterogeneous immune response in the diabetic group. On the other hand, among the non-diabetic obese ($n = 13$) group the IgG levels are clustered between 9 to 10 months (Fig D vs H). The IgG levels of both diabetic and non-diabetic subjects show variance, regardless of any factors.

IgG levels concerning diabetes status

IgG levels concerning the duration of diabetes did not show any statistical difference ($p = 0.237$). IgG antibody levels were looked into BMI groups; normal, overweight, and obese subjects with 11.84 ± 9.18 , 12.47 ± 8.68 , and 18.54 ± 14.33 BAU/mL ($p = 0.037$) (Table 3). Among all subjects, the obese subgroup had significantly high IgG compared to the normal-weight and overweight groups ($p = 0.029$) (Fig 2a). The difference with the overweight group was relatively high ($p = 0.053$). Among diabetics, the obese subgroup had significantly higher IgG levels compared to normal ($p = 0.025$) and overweight ($p = 0.033$) subgroups (Fig 2b). Among the non-diabetic subjects, IgG levels did not show significant differences ($p = 0.648$) (Table 3).

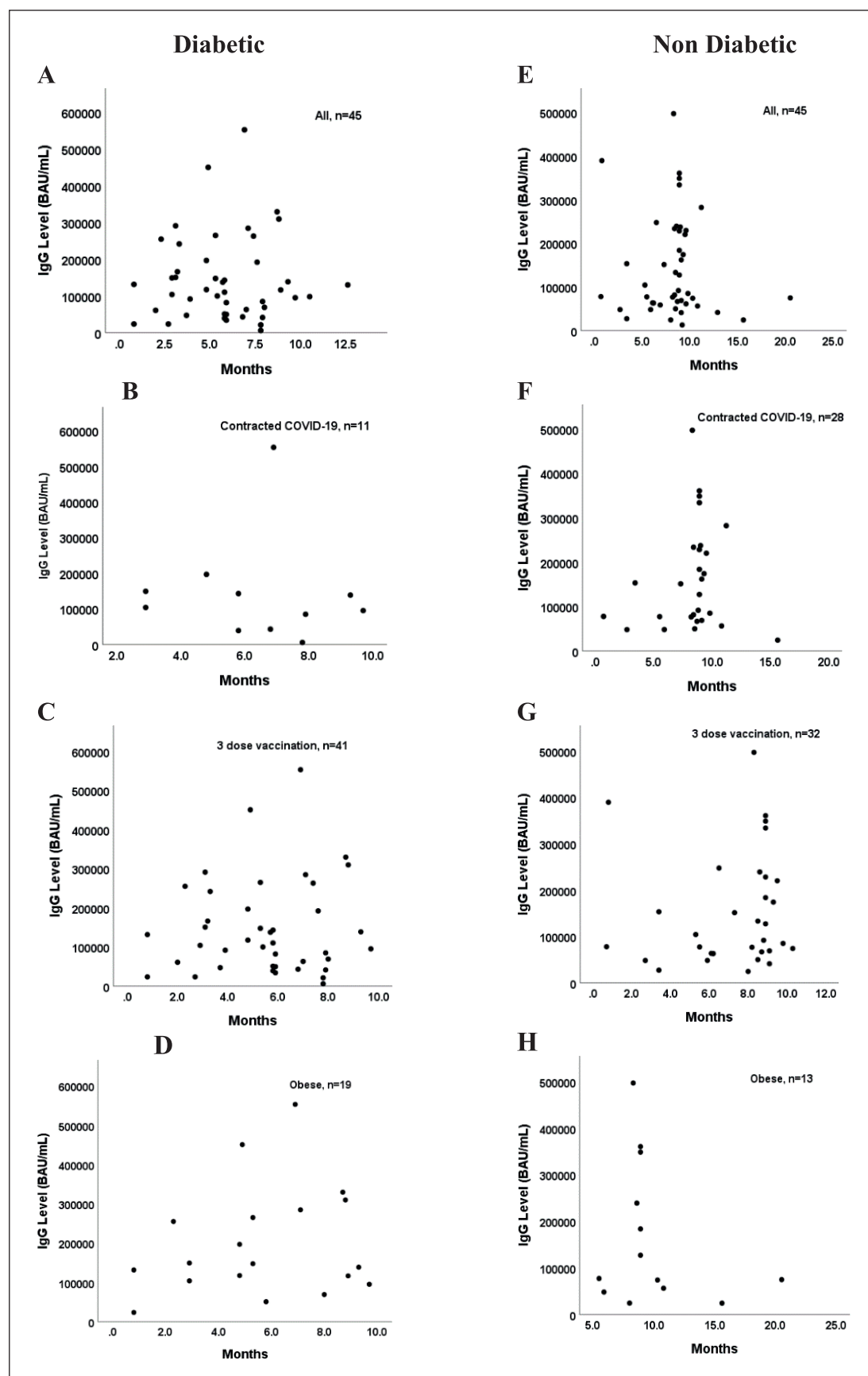


Fig 1: SARS-Cov-2 IgG levels among all subjects of diabetic and Non diabetic (**A** vs **E**), COVID-19 contracted (**B** vs **F**), 3 dose vaccination (**C** vs **G**), and obesity (**D** vs **H**) of diabetic and Nondiabetic subjects.

Table 3: SARS-CoV-2 IgG antibody status of the subjects

Variables	All (N=90) BAU/mL	p value	Diabetic BAU/mL (N=45)	p value	Non-diabetic BAU/mL (N=45)	p value
a) COVID-19 Infection						
Yes			14.15±14.75	0.916	16.26±11.80	0.146
No	-	-	14.58±10.69		11.12±10.41	
b) Number of vaccine doses						
1 dose	10.11±3.45	0.594	12.16±2.59		7.04±1.61	
2 doses	12.91±9.63		13.05		12.90±10.10	
3 doses	14.93±12.08		14.68±12.16		15.26±12.17	
c) Duration of diabetes						
≤5 yrs	-	-	14.99±11.05	0.237	-	-
5.1-10 yrs			16.19±13.71			
>10 yrs			7.90±5.05			
d) BMI range (Kg/m ²)						
Normal	11.84±9.18	0.037	11.004±7.93	0.029	12.53±10.26	0.648
Overweight	12.47±8.68		9.72±7.61		14.63±9.12	
Obese	18.54±14.33		19.97±13.92		16.46±15.23	

Results were expressed as mean±SD. Statistical difference for (a), (c), and (d) was calculated by using student's unpaired 't' test. A $p < 0.05$ was taken as level of significance. ANOVA test was carried out to calculate statistical difference of (b) and (e). A $p < 0.05$ was taken as level of significance

DISCUSSION

Acquired immunity, particularly humoral immunity following either natural infection or vaccination, is crucial in protecting subjects from reinfection by the same pathogen. However, the immune response following infection or vaccination is often influenced by several factors, including nutritional status, chronic conditions like obesity, immunosuppressive medications, diabetes and chronic renal disease^{21,22}. This study was aimed to look at the SARS-CoV-2 IgG status among the diabetic and non-diabetic subjects, all

of who have received vaccination against COVID-19. SARS-CoV-2 IgG antibody levels (mean±SD, BAU/mL) in study subjects were pronounced compared to the previous reports from 10-30,000 BAU/mL²³⁻²⁷. The IgG level, however, did not show statistical difference between diabetic and non-diabetic groups (Table 3). This precludes the notion that diabetes lacks in immune response to SARS-CoV-2 and in general²⁴⁻²⁶. The data suggest that the subjects had strong immune responses following vaccination, independent of diabetic status. Subjects with diabetes for more than 10 years had notably lower antibody levels compared to those with

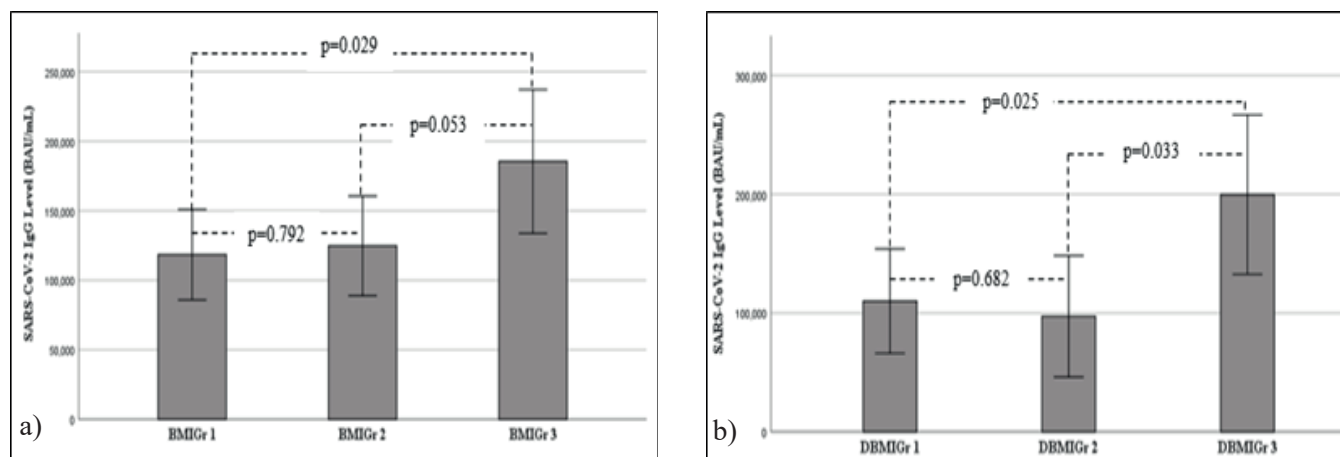


Figure 2. (a) SARS-CoV-2 IgG level of the BMI groups of all the subjects. Statistical difference was calculated by using the student's unpaired 't' test. A $p < 0.05$ was taken as the level of significance. BMI Gr1, normal BMI (< 23); BMI Gr2, overweight (23.1-24.9); and BMI Gr3, obese (≥ 25). **(b)** SARS-CoV-2 IgG level of the BMI groups of the diabetic subjects. Statistical difference was calculated by using the student's unpaired 't' test. A $p < 0.05$ was taken as the level of significance. BMI Gr1, normal BMI (< 23); BMI Gr2, overweight (23.1-24.9); and BMI Gr3, obese (≥ 25).

shorter durations of diabetes, although the difference was not statistically significant (Table 3). This pattern is in congruence with a report by Sourij et al. 2022, which also observed no significant immunogenic response in diabetic subjects after vaccination. This further prioritizes that the immune response of the individual is affected based on their genetic diversity, presence of any underlying condition, or antigen exposure level²⁸.

Individual SARS-COV-2 IgG antibodies were further looked into considering multiple factors, where a significant variability was observed among them. It was resolved that the immune responses were heterogeneous, indicating a wide diversity in antibody concentrations in subjects who received the vaccine within a comparable timeframe. Among the 45 diabetic subjects, 11 had IgG levels below 50,000 BAU/mL, whereas 9 out of 45 non-diabetic subjects demonstrated IgG concentrations below the cut-off value which suggests that IgG levels may vary due to individual immune responses, influenced by metabolic and health conditions²⁹. Additionally, the presence of IgG antibodies after vaccination was found elevated for more than eight months, independent of the number of doses and vaccine types received (Fig 1).

To further explore the heterogeneity of immune response, antibody levels were compared among subjects with different BMI groups, where antibody levels were significantly higher in the obese group (Fig 2.a). In the

diabetic group, vaccine seroconversion was pronounced compared to the normal weight group (Fig 2.b), while in the non-diabetic group, the response was similar across BMI categories. It is understood that diabetes is an inflammation condition and obesity put added risk to the condition. This finding is consistent with previous reports which demonstrated variable degrees of seroconversion response among diabetic population^{30,31}. Another report suggested a possibility of yet unexplained situations where subjects with obesity, may have an impact on IgG level³². However, other reports did not show any association between SARS-CoV-2 IgG level and obesity^{27,33}. However, it is worth noting that the obese group of the study had a BMI below a certain threshold, indicating that they were not morbidly obese and that the BMI range was in line with regional standards.

In addition to examining their IgG antibody level, the history of COVID-19 infection between diabetic and non-diabetic subjects was also observed. Among the diabetic subjects, a smaller percentage was infected with COVID-19 compared to non-diabetic subjects, suggesting that diabetic subjects may have engaged in fewer outdoor activities, possibly due to stricter adherence to social distancing measures. This result highlights that quarantine proves to be an effective approach to limit COVID-19-like infectious diseases (Table 2), even when applied to vulnerable population^{18,20,34}.

CONCLUSION

Vaccination against SARS-CoV-2 showed a pronounced immune response, as validated by the measurement of IgG in diabetic and non-diabetic subjects. However, no statistical difference between the two groups was observed. Increasing the number of vaccine doses correlated with increasing antibody levels, suggesting a dose-dependent effect. Interestingly, obese subjects demonstrated higher antibody response, particularly within the diabetic group, underscoring the role of obesity as a negative modulating factor. Furthermore, diabetic patients were less frequently contracted with COVID-19 compared to non-diabetic subjects, possibly due to low exposure to populated settings. These findings shed light on the complex and heterogeneous interplay

between diabetes, obesity, and immune responses to COVID-19 vaccination, offering valuable insights for tailoring vaccination strategies in vulnerable population

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