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ORIGINAL ARTICLE

Antibody levels in people with diabetes after one dose of the ChAdOx1 nCoV-19 (AZD1222) vaccine

Vimonsri Rangsrisaeneepitak[1] · Thachanun Porntharukchareon[1] · Bothamai Dechates[1] · Supamas Sirisreetreerux[1] · Kriangkrai Tawinprai[2]

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Abstract

Patients with diabetes and coexistent coronavirus disease 2019 (COVID-19) have a higher risk of COVID-19 complications. Therefore, it is critical that sustained and effective immunogenicity against COVID-19 is achieved in such patients. This study evaluates the antibody response for 56 days after the first dose of the AZD1222 vaccine in subjects with and without diabetes to assess the potential risk of delaying the second dose. This study included 282 people who received one dose of AZD1222. The geometric mean concentration of antibodies specific for severe acute respiratory syndrome coronavirus 2 IgG at 56 days was significantly ($P < 0.001$) lower in people with type 2 diabetes mellitus (T2D; 15.13 BAU/mL, 95% confidence interval [CI] = 10.7–21.4) than in those without diabetes (40.20 BAU/mL, 95% CI = 33.43–48.36), as confirmed by a geometric mean ratio of 0.37 (95% CI = 0.25–0.54). Weaker immune responses were also observed in diabetic patients ≥ 65 years old (10.09 BAU/mL, 95% CI = 6.09–16.71) compared with their younger counterparts (22.31 BAU/mL, 95% CI = 13.98–35.59, $P = 0.034$). People with T2D had weaker antibody responses than those without diabetes after the first dose of AZD1222. Older age was associated with weaker antibody responses in elderly patients with diabetes.

Keywords COVID-19 · SARS-CoV-2 · Type 2 diabetes · AZD1222 · Antibodies · Humoral response

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), was first reported in December 2019, and it has subsequently spread worldwide. Patients with diabetes and coexistent COVID-19 have higher risks of complications, hospitalizations, intensive-care unit admission, morbidity, and mortality [1, 2]. Because of the increased risk of poor outcomes in patients with coexistent diabetes, diabetes is one of the comorbidities considered a priority for vaccination against COVID-19 by WHO.

The ChAdOx1 nCoV-19 vaccine (AZD1222), developed by Oxford University and AstraZeneca, is one of the COVID-19 vaccines used in Thailand. It consists of the replication-deficient chimpanzee adenoviral vector ChAdOx1 carrying the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. AZD1222 was approved by Thailand's Food and Drug Administration (FDA) for emergency use in January 2021 [3]

Immunogenicity and vaccine efficacy after the second dose of AZD1222 were higher in patients with prime–boost intervals of at least 12 weeks than in those with intervals shorter than 6 weeks [4]. Therefore, an 8–12-week interval between the two doses has been recommended. Although longer gaps between doses have been shown to improve the efficacy and strategies with a delayed second dose have been discussed during the period of limited vaccine supply, the potential risk of delaying the second dose raises concerns. This strategy might have negative consequences in people with low levels of immunity in this period, resulting in a higher risk of breakthrough infection.

Patients with diabetes are vulnerable to severe COVID-19. Immune response data after a single dose of the

✉ Kriangkrai Tawinprai
Kriangkrai.taw@cra.ac.th

[1] Endocrinology and Metabolism Unit, Department of Medicine, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand

[2] Infectious Disease Unit, Department of Medicine, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand

AZD1222 vaccine in patients with diabetes are limited. This study investigated antibody responses at 56 days after the first dose of the AZD1222 vaccine in patients with and without diabetes in Thailand.

Methods

Study design and participants

This clinical study evaluated immune responses after the first dose of the AZD1222 vaccine in patients with diabetes. Patients with diabetes who visited Chulabhorn Hospital were invited to participate. Participants who volunteered to receive the AZD1222 vaccine were enrolled between June 8, 2021 and July 12, 2021. Healthcare personnel in our institute mostly had no underlying disease, and they were enrolled as age- (within 5 years) and gender-matched controls. All subjects provided informed consent before participating in the study. Demographic data, comorbidities, diabetes complications, body mass index (BMI), and glycated hemoglobin (HbA1c) levels over 3 months were collected from patients and their medical records. Obesity is defined as BMI of at least 25 kg/m^2 in the Asian population.

Participants with a history of COVID-19 infection and those who had received other COVID-19 vaccines were excluded. Additional key exclusion criteria were a history of acute illness or blood transfusion in the last 3 months, pregnancy, and breastfeeding.

Procedure

A single injection of 0.5 mL of the ChAdOx1 vaccine was given to each participant intramuscularly in the deltoid muscle. Participants were observed in the clinic for 30 min after the vaccination procedure and asked to record any reactogenicity using a mobile application on days 1 and 7 after vaccination.

The ChAdOx1 vaccine was prescribed with a dosing interval of 12 weeks. Six milliliters of blood were collected on day 0 before the first vaccine dose and 56 ± 7 days (8 weeks) after the first dose. Antibodies (total) against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein were measured using an FDA-approved method (Roche Elecsys, Roche Diagnostics International).

Outcome

The primary outcome was the geometric mean concentration (GMC) of anti-RBD antibodies after the first vaccine dose in participants with and without diabetes on day 56, and the GMC was compared between the groups using the geometric mean ratio (GMR). The secondary outcomes were the seroconversion rate in the groups and factors associated with immune responses and the seroconversion rate in patients with diabetes.

Sample size calculation

Based on a study of robust antibody levels in subjects with and without diabetes after BNT162b2 mRNA COVID-19 vaccination, the GMC was 79 BAU/mL in subjects with diabetes, versus 87 BAU/mL in subjects without diabetes. The standard deviation was 19.5. The sample size was calculated to achieve a power of 80% with a significance level of 5% (alpha = 0.05) [5, 6]. The number of subjects needed was estimated to be 94. This estimation was calculated based on an assumption that 10% of the participants would be lost to follow-up.

Statistical analysis

The results are presented as the mean and standard deviation or median and interquartile range (IQR) according to whether they were normally or non-normally distributed. The anti-RBD antibody concentration was summarized as the GMC and 95% confidence interval (CI). The GMC was compared between the groups using a multiple linear regression model. The seroconversion rate was compared between the groups using a multiple logistic regression model. Statistical analyses were performed using STATA/SE version 16. A P value less than 0.05 indicated statistical significance.

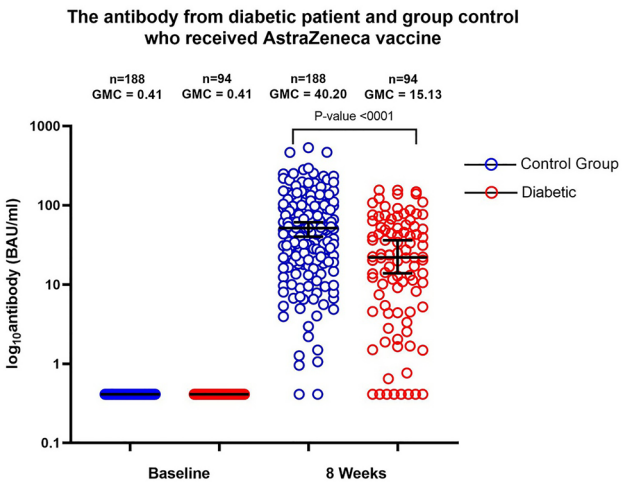

Fig. 1 Anti-severe acute respiratory syndrome coronavirus 2 antibody response after a single dose of the AZD1222 vaccine in individuals with type 2 diabetes and healthy controls

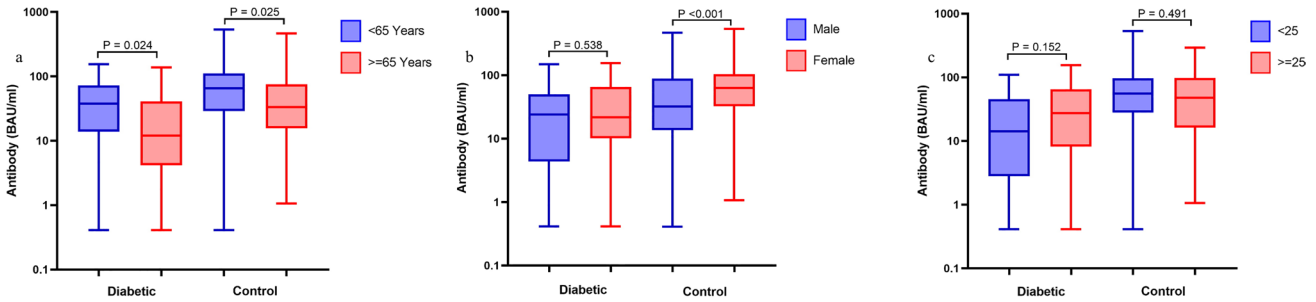

Figure 2. Serological response in individuals with type 2 diabetes and healthy controls according to (2a) Age, (2b) Gender, (2c) Obesity (BMI < or >= 25 kg/m2)

Fig. 2 Serological response in individuals with type 2 diabetes and healthy controls according to (2a) Age, (2b) Gender, and (2c) Obesity (BMI < or > = 25 kg/m2)

Results

Baseline characteristics

Between June 8, 2021 and Jul 12, 2021, 94 patients with diabetes and 188 age- and gender-matched healthcare personnel were enrolled in the study. The baseline characteristics are presented in Table 1. Participants with diabetes were all type 2 diabetes, aged between 30 and 83 years (with the median age of 64 years [IQR 60–69]). More than two-thirds (71%) of these patients were at least 60 years old. The participants with diabetes included 51 men and 43 women. The median BMI was 25.37 (IQR 23.28–28.00), and 54.26% of patients with diabetes were considered obese. The median BMI of age- and gender-matched healthcare personnel was 24.81 (IQR 22.83–27.43). There is no statistically significant difference between two groups.

The diabetes (type 2 diabetes [T2D]) cohort had a median HbA1c level of 6.8 ± 1.7, and good diabetes control, as indicated by HbA1c levels less than 7, was identified in 56.32% of patients. Insulin usage was noted in 21.59% of patients (19). Diabetic retinopathy and chronic kidney disease (defined as glomerular filtration rate [GFR] calculated by CKD-EPI formula < 60) were identified in 18 and 30 participants, respectively.

Quantitative antibody readings after first dose vaccination

Results of multiple regression analysis for SARS-CoV-2 IgG antibodies in people with or without diabetes were shown in Table 2, Figs. 1 and 2. The GMC of SARS-CoV-2 IgG antibodies at 56 days was significantly ($P < 0.001$) lower in patients with diabetes (15.13 BAU/mL, 95% CI = 10.7–21.4) than in age- and gender-matched controls (40.20 BAU/mL, 95% CI = 33.43–48.36), and the GMR was 0.37 (95% CI = 0.25–0.54). It was also found that obesity status did not significantly affect the level of IgG antibodies.

In participants with diabetes, SARS-CoV-2 IgG antibody levels did not significantly differ between men and women ($P = 0.715$). Weaker immune responses were noted in patients ≥ 65 years old than in their younger counterparts (10.09 BAU/mL [95% CI = 6.09–16.71] vs. 22.31 BAU/mL [95% CI = 13.98–35.59], $P = 0.034$). The obesity status, HbA1c level, and presence of diabetic complications did not significantly affect antibody levels. The serological findings are summarized in Table 3.

SARS-CoV2 IgG antibody levels in age- and gender-matched control were also lesser in patients 65 years of age or older compared to those younger ages (32.61 BAU/ml [95% CI = 25.60, 41.55] vs. 49.56 BAU/ml [95% CI = 37.58–65.37], P = 0.011). Females' SARS-CoV2 IgG antibody level was

Table 1 Clinical characteristics of individuals with type 2 diabetes and age- and gender-matched controls

Variable	DM	Control
Age, median (IQR)	64 (60.00,69.00)	64.50 (61.00,69.50)
Gender, *n* (%)		
Male	51 (54.26%)	102(54.26%)
Female	43 (45.74%)	86 (45.74%)
Weight (kg), median (IQR)	65.75 (58.60,78.00)	68.70 (59.10,78.00)
BMI (kg/m^2), median (IQR)	25.37(23.28,28.00)	24.81 (22.83,27.43)
Obesity, *n* (%)	51 (54.26%)	88 (49.16%)
HbA1c, median (IQR)	6.8 (6.30,8.00)	–
HbA1c < 7, *n* (%)	49 (56.32%)	–
DR, *n* (%)	18 (22.50%)	–
CKD (GFR < 60), *n* (%)	30 (33.71%)	NA
Insulin usage, *n* (%)	19 (21.59%)	–

IQR interquartile range, *HbA1c* glycated hemoglobin, *BMI* body mass index, *SD* standard deviation, *DR* diabetic retinopathy, *CKD* chronic kidney disease, *GFR* glomerular filtration rate

Table 2 Multiple linear regression analysis for SARS-CoV-2 IgG antibodies in type 2 diabetes and age- and gender-matched controls

	N (%)	Immunity (BAU/ml) Geometric ratio (95% CI)	(Geometric mean 95% CI)	*P* value
DM				< 0.001
No	188 (66.67)	40.20 (33.42, 48.36)	Ref.	
Yes	94 (33.33)	15.13 (10.70, 21.40)	0.37 (0.25, 0.54)	
Age group				< 0.001*
< 65	142 (50.35)	37.84 (29.57, 48.43)	Ref.	
> = 65	140 (49.65)	22.18 (17.33, 28.39)	0.54 (0.39, 0.75)	
Sex				0.001*
Female	129 (45.74)	38.43 (30.06, 49.13)	Ref.	
Male	153 (54.26)	22.91 (17.91, 29.30)	0.56 (0.40, 0.78)	
BMI				0.490
< 25	134 (49.08)	28.00 (21.34, 36.74)	Ref.	
> = 25	139 (50.92)	29.11 (22.82,37.13)	1.13 (0.80, 1.57)	

BMI body mass index, *CI* confidence interval

*Age- and gender-matched controls

Table 3 Univariate and multivariate analyses of variable associate with GMC in individuals with type 2 diabetes

	GMC	95% CI	Univariate analysis		Multivariate analysis	
			Geometric ratio (95% CI)	*P* value	Geometric ratio (95% CI)	*P* value
Age				0.022		0.034
< 65	22.31	13.98–35.59	Ref.		Ref.	
≥ 65	10.09	6.09–16.71	0.45 (0.23, 0.89)		0.44 (0.21, 0.94)	
Gender				0.538		0.715
Female	17.03	10.08–28.76	Ref.		Ref.	
Male	13.7	8.51–22.05	0.80 (0.40, 1.62)		1.17 (0.50, 2.77)	
BMI (kg/m^2)				0.152		0.141
< 25	11.52	6.9–19.22	Ref.		Ref.	
≥ 25	19.03	11.8–30.7	1.65 (0.83, 3.30)		1.97 (0.79, 4.87)	
HbA1c				0.933		0.622
HbA1c < 7	15.48	9.29–25.63	Ref.		Ref. 1.25	
HbA1c ≥ 7	14.97	8.72–25.7	0.97 (0.47, 2.01)		(0.51, 3.02)	
Documented DR	18.23	9.55–34.8	1.27 (0.61, 2.67)	0.519	1.43 (0.56, 3.60)	0.448
CKD (GFR < 60)	11.19	5.79–21.64	0.69 (0.32, 1.48)	0.333	0.80 (0.30, 2.13)	0.648
Insulin use	17.74	7.28–43.2	1.33 (0.53, 3.35)	0.537	0.98 (0.28, 3.39)	0.968

BMI, body mass index; HbA1c, glycated hemoglobin; DR, diabetic retinopathy; CKD, chronic kidney disease; GFR, glomerular filtration rate; CI, confidence interval; GMC, geometric mean concentration

57.74 BAU/mL [95% CI = 46.32, 71.98], which was significantly higher than the SARS-CoV2 IgG antibody level of males that turned out to be to 29.63 BAU/mL [95% CI = 22.51, 38.99] ($p < 0.001$). Antibody levels were also not significantly different ($p = 0.905$) between obesity status (Table 4).

When age-, gender-, and obesity status-subgroup analyses were conducted in people with or without diabetes, antibody response was found to be lower in all diabetic subgroups than that in non-diabetic subgroups ($P < 0.001$).

Table 4 Multiple linear regression analysis for SARS-CoV-2 IgG antibodies in healthy controls

	N (%)	Immunity (BAU/ml) (geometric mean 95%CI)	Geometric ratio (95% CI)	P _value
Age group				0.011
< 65	94 (50.00)	49.56 (37.58, 65.37)	Ref.	
> = 65	94 (50.00)	32.61 (25.60, 41.55)	0.63 (0.44, 0.90)	
Sex				< 0.001
Female	86 (45.74)	57.74 (46.32, 71.98)	Ref.	
Male	102 (54.26)	29.63 (22.51, 38.99)	0.50 (0.34, 0.73)	
BMI				0.905
< 25	91 (50.84)	42.60 (31.99, 56.72)	Ref.	
> = 25	88 (49.16)	37.23 (28.69, 48.33)	0.98 (0.66, 1.44)	

BMI, body mass index; CI, confidence interval

Seroconversion of antibodies after the first vaccine dose

Before vaccination, all patients were confirmed to be seronegative for anti–SARS-CoV-2 spike protein IgG antibodies (level < 0.8 U/mL). Nearly 96% (95.7%) of all participants developed positive antibody responses approximately 8 weeks after the first dose of AZD1222. The seroconversion rate was higher in the control group than in the diabetes group (odds ratio = 11.07 [95% CI = 2.37–51.64], $P = 0.002$). The factors of age, gender, HbA1c levels, and diabetic complications did not affect the outcome for both people with or without diabetes.

Reactogenicity

Adverse events within the first day and after 2–7 days are presented in Table 5. Injection site reactions were more common in patients with diabetes than in healthy controls within the first 24 h (15 [15.95%] vs. 6 [31.91%], $P < 0.001$). No severe local reactions were reported in patients with diabetes. Headache, fatigue, and myalgia were commonly reported systemic reactions, and their incidence did not differ between the groups. However, a few participants developed adverse events 2–7 days after vaccination, and their rates did not differ between the groups.

Discussion

By monitoring serum anti-SARS-CoV-2 IgG antibody levels, this study provided evidence of a lower humoral immune response to the first dose of AZD1222 in patients with T2D than in age- and gender-matched controls at 56 days post-vaccination. Older age was associated with weaker immune responses for individuals with or without diabetes. Among patients aged > 65 years, those with diabetes were associated with weaker immune responses compared to those in the healthy control group.

Lower seroconversion rates and reduced antibody concentrations after the first dose of AZD1222 have been noted in particular risk groups, including patients with diabetes. However, mRNA vaccines were also reported to have lower effectiveness in patients with diabetes [7].

Following the administration of adenoviral vector vaccines, adenoviral vector interacts with a specific receptor and enters a host cell. Viral genomes are then released into the nucleus and induce transgene products. When transgene products are expressed in non-immune cells such as muscle cells, transgene proteins are then released and absorbed by antigen-presenting cells. Specific antibodies from B cells are consequently produced. The activation of B cells and their transformation into antibody-secreting plasma cells are triggered by antigens and usually require helper T cells (CD4 + Tcells). When transgenes are expressed in immune cells such as dendritic cells and macrophage, cross presentation of antigens occurs, which is then leading to mainly cytotoxic T cell (CD8 + T cells) induction [8].

Several hypotheses of molecular mechanism postulate that individuals with diabetes have a weaker antibody response compared to those without diabetes. First, reduced numbers of dendritic cells are observed in both type1 and type 2 diabetes. These dendritic cells play a key role in antigen-presenting cells and stimulating an adaptive immune response. Second, previous studies have shown that CD4 + T lymphocyte functions are impaired. Patients with diabetes have deficiencies in memory CD4 + and Th17 response, which are likely the result of hyperglycemia and expression of advanced glycation end products (RAGE) [9]. Reduced tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interferon-γ (IFNγ) from CD4 + T lymphocyte were also observed after vaccine administration in type 2 diabetes [11]. T2DM patients with poor metabolic control have decreased numbers of both myeloid and plasmacytoid dendritic cells. In addition, other defects in immunity, including reduced

Table 5 Adverse reactions at day 1 and at 2–7 days after AZD1222 vaccine in individuals with type 2 diabetes and healthy controls

	Day1			Day2-7		
	DM	Control	*P* value	DM	Control	*P* value
Injection site reaction			0.000[2]			1.000[2]
No	79 (84.04)	182 (96.81)		92 (97.87)	183 (97.34)	
Mild	9 (9.57)	3 (1.60)		2 (2.13)	5 (2.66)	
Moderate	6 (6.38)	2 (1.06)		0 (0.00)	0 (0.00)	
Severe	0 (0.00)	1 (0.53)		0 (0.00)	0 (0.00)	
Fever			0.528[2]			0.778[2]
No	89 (94.68)	172 (91.49)		93 (98.94)	182 (96.81)	
Mild	4 (4.26)	7 (3.72)		1 (1.06)	5 (2.66)	
Moderate	1 (1.06)	8 (4.26)		0 (0.00)	1 (0.53)	
Severe	0 (0.00)	1 (0.53)		0 (0.00)	0 (0.00)	
Headache			1.000[2]			0.801[2]
No	84 (89.36)	169 (89.89)		93 (98.94)	184 (97.87)	
Mild	6 (6.38)	12 (6.38)		0 (0.00)	2 (1.06)	
Moderate	4 (4.26)	7 (3.72)		1 (1.06)	2 (1.06)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Fatigue			0.093[2]			0.852[2]
No	79 (84.04)	172 (91.49)		92 (97.87)	182 (96.81)	
Mild	8 (8.51)	7 (3.72)		1 (1.06)	4 (2.13)	
Moderate	4 (4.26)	8 (4.26)		1 (1.06)	2 (1.06)	
Severe	3 (3.19)	1 (0.53)		0 (0.00)	0 (0.00)	
Myalgia			0.716[2]			0.778[2]
No	80 (85.11)	167 (88.83)		93 (98.94)	182 (96.81)	
Mild	9 (9.57)	13 (6.91)		1 (1.06)	5 (2.66)	
Moderate	5 (5.32)	7 (3.72)		0 (0.00)	1 (0.53)	
Severe	0 (0.00)	1 (0.53)		0 (0.00)	0 (0.00)	
Nausea or Vomiting			0.487[2]			0.404[2]
No	90 (95.74)	183 (97.34)		94 (100.00)	184 (97.87)	
Mild	4 (4.26)	5 (2.66)		0 (0.00)	2 (1.06)	
Moderate	0 (0.00)	0 (0.00)		0 (0.00)	2 (1.06)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Diarrhea			1.000[2]			0.536[2]
No	91 (96.81)	182 (96.81)		92 (97.87)	185 (98.40)	
Mild	3 (3.19)	6 (3.19)		1 (1.06)	3 (1.60)	
Moderate	0 (0.00)	0 (0.00)		1 (1.06)	0 (0.00)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Other			1.000[2]			
No	94 (100.00)	187 (99.47)		94 (100.00)	188 (100.00)	–
Mild	0 (0.00)	1 (0.53)		0 (0.00)	0 (0.00)	
Moderate	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
Severe	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	

[1] Pearson chi-square [2] Fisher's exact test

lymphocyte proliferative response, impaired monocyte/macrophage, and neutrophil function, have been associated with hyperglycemia and insulin resistance [10].

The vaccination schedule for AZD1222 in most countries is two doses separated by a 12-week interval. However, the weaker immune response in patients with diabetes at 8 weeks after single-dose vaccination suggests an increased risk of severe infection before a booster dose is received. Therefore, a shorter period between vaccine doses might be beneficial.

Although evidence suggests that glycemic control strongly affects the efficiency of the immune response after COVID-19 vaccination in patients with diabetes [11], HbA1c levels had no significant effect on IgG levels in our

study. However, HbA1c levels were not measured at the time of vaccination in this study, and thus, the results of this study might not have accurately reflected the patients' glycemic status. Obesity, which is often accompanied by T2D, is also considered to impair the immune response to vaccination [12]. However, there was no significant difference in IgG antibody levels according to the obesity status among patients with diabetes. Nevertheless, patients ≥ 65 years old with diabetes appeared to have weaker immune responses after the first dose of AZD1222 than their younger counterparts. These findings support the need for a shorter interval between vaccine doses in elderly patients with diabetes.

Limitation

This study had several limitations. First, this was a single-center study. Second, participants in the control group were healthcare personnel, and thus, natural immunity may have been a confounding factor. Finally, we did not monitor neutralizing antibody levels, which are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. However, antibodies against the spike protein RBD have been revealed to confer neutralizing activity against SARS-CoV-2 with an optimized cutoff.

Conclusion

People with diabetes had weaker antibody responses than individuals without diabetes after the first dose of AZD1222. Older patients with diabetes also displayed weaker antibody responses. Our findings support the need for appropriate booster doses in patients with diabetes, especially among elderly patients.

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Declarations

Conflict of interest The authors declare that the research was conducted with no conflict of interest. The study protocol, case records form, and consent form were reviewed and approved by the Ethics Committee for Human Research of Chulabhorn Research Institute (056/2564) on June 7, 2021. This trial was registered with thaiclinicaltrials.org (TCTR20211228003), and the protocol conformed to the principles of the Declaration of Helsinki.

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