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Original Article

Reduced Immunogenicity of COVID-19 Vaccine in Obese Patients with Type 2 Diabetes: A Cross-Sectional Study

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The global pandemic of coronavirus infection 2019 (COVID-19) was an unprecedented public health emergency. Several clinical studies reported that heart disease, lung disease, diabetes, hypertension, dyslipidemia, and obesity are critical risk factors for increased severity of and hospitalization for COVID-19. This is largely because patients with these underlying medical conditions can show poor immune responses to the COVID-19 vaccinations. Diabetes is one of the underlying conditions most highly associated with COVID-19 susceptibility and is considered a predictor of poor prognosis of COVID-19. We therefore investigated factors that influence the anti-SARS-CoV-2 spike IgG antibody titer after three doses of vaccination in patients with type 2 diabetes. We found that obesity was associated with low anti-SARS-CoV-2 spike IgG antibody titers following three-dose vaccination in type 2 diabetics. Obese patients with type 2 diabetes may have attenuated vaccine efficacy and require additional vaccination; continuous infection control should be considered in such patients.

Key words: obesity, type 2 diabetes, COVID-19, vaccination

The global pandemic of coronavirus infection 2019 (COVID-19) is an unprecedented public health emergency that has disrupted our lives for more than four years [1]. The clinical manifestations of COVID-19 are diverse. Most patients with COVID-19 present with asymptomatic or moderate symptoms, but the clinical manifestations of COVID-19 range from mild respiratory illness to severe pneumonia, multiple organ failure, and in some cases death [2]. Although many clinical studies have reported risk factors contributing to susceptibility, severity, and mortality of COVID-19, in the initial stages of the epidemic, it was considered that heart disease, lung disease, diabetes, hypertension, dyslipidemia, and obesity were important risk factors for severity and hospitalization. Among these diseases, diabetes was recognized as one of the underlying conditions most highly associated with COVID-19 susceptibility and was considered a predictor of poor prognosis of COVID-19 [3].

Effective and safe vaccines against SARS-CoV-2 are essential to prevent severe disease and ultimately enable social and economic recovery. Because the vaccine stimulates an immune response that recognizes SARS-CoV-2, vaccination is the best way to protect people and reduce viral infections. The memory cell response

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induced by the COVID-19 vaccine induces Th1 and sustained germinal center responses, leading to strong cellular and humoral immunity [4]. In Japan, mRNA-based vaccines such as BNT162b and mRNA-1273 have been the main vaccines used for COVID-19 prevention. Several publications have reported that patients with underlying medical conditions such as hypertension, diabetes, and obesity have poor immune response to vaccination [3, 5], although there is debate regarding the degree of impact of these different conditions. Few reports have examined the efficacy of vaccines in patients with type 2 diabetes. In recent reports, therefore, we have been investigating factors that influence the anti-SARS-CoV-2 spike IgG antibody titer after three doses of vaccination in patients with type 2 diabetes. We found that obesity was associated with low anti-SARS-CoV-2 spike IgG antibody titers following three doses of vaccination in patients with type 2 diabetes.

Materials and Methods

Study participants. This cross-sectional study included 117 patients with type 2 diabetes who were recruited between December 3, 2021 and November 30, 2022 at Okayama University Hospital. All patients were within 3 months of receiving the third dose of the BNT162b2 or mRNA-1273 vaccination. 84.1% of the participants had been vaccinated with BNT162b2. Type 2 diabetes was defined as a fasting blood glucose level ≥126 mg/dL (7.0 mmol/L) and/or HbA1c ≥6.5% or treatment with anti-diabetes medication. The exclusion criteria were (1) pregnancy, (2) treatment with immunosuppressants, (3) cancer, or (4) confirmed COVID-19. All participants provided written informed consent. The study protocol (No. 21112-044) was approved by the ethics committee of Okayama University and was conducted in accordance with the Declaration of Helsinki.

Clinical and biochemical measurements. BMI was calculated using the following formula: body weight (kg) / height^2 (m^2). Medical history, current medication data, and laboratory data were collected from the medical charts of each patient. eGFR was calculated using the following formula modified for Japanese subjects: eGFR (mL/min/1.73 m^2) = 194 × s-Cr (mg/dL)$^{-1.094}$ × age (yr)$^{-0.287}$ (× 0.739 for females). Diabetic retinopathy (DR) was diagnosed using standard fundus examinations conducted by ophthalmologists. Diabetic nephropathy (DN) was defined as a urine albumin-to-creatinine ratio (UACR) of ≥30 mg/gCr. The prevalence of microvascular complications was assessed based on the presence of DR or DN.

The Mokobio SARS-CoV-2 IgM & IgG Quantum Dot immunoassay (Mokobio Biotechnology R&D Center, Rockville, MD) was used to measure the whole-blood concentration of an IgG targeting the receptor-binding domain of the SARS-CoV-2 spike protein as described previously [6]. Briefly, 30 μl of whole blood was applied to the assay cassette, followed by 100 μl of loading buffer, and the cassette was incubated for 15 min at room temperature. The fluorescence signal was semi-quantified by an immunofluorescence analyzer. According to the manufacturer's instructions, the specificity of the test was 99.7%, with a lower limit of 30 U/mL and an upper limit of 30,000 U/mL. Five cases were excluded because more than 30,000 U/mL were determined to be invalid.

Statistical analysis. Continuous variables were presented as the mean ± standard deviation or, if variables were not normally distributed, as the median (25-75th percentile). Categorical variables were expressed as absolute numbers or percentages. Differences between two groups in each separate experiment were analyzed using Student's *t*-test or non-parametric Mann-Whitney test. Spearman's rank correlation was performed to determine correlation coefficients. Multivariable logistic regression analysis was used to evaluate possible effects on the SARS-CoV-2 antibody titers. All statistical analyses were performed using SPSS Statistics version 26 (IBM, Armonk, NY, USA). *P* values of < 0.05 were considered to be significant.

Results

Baseline characteristics of the study participants. A total of 117 patients with type 2 diabetes were included in this study. Baseline characteristics are shown in Table 1. The median age was 62 years (interquartile range [7], 52-72), and the proportions of patients aged 30-39, 40-49, 50-59, 60-69, 70-79, and 80-89 years were 7.7%, 12.8%, 20.5%, 25.6%, 20.5%, and 12.0%. Median BMI was 26.24 kg/m^2 (IQR, 22.23-30.7). The male proportion was 46.2%. There were 72 cases of hypertension and 81 cases of dyslipidemia. Overall, the prevalences of DR and DN were 22.2% and 28.3%, respectively. The prevalences of cardiovascular disease, stroke, and peripheral arterial disease were 8.5%, 5.1%, and 1.7%,

Table 1 Characteristics of patients with type 2 diabetes

Variables			T2D ($n=117$)
Age (years)			62 (52–72)
Gender (%)	Men		46.2
	Women		53.8
Alcohol history (%)			28.0
Smoking status (%)	Smoker		11.2
BMI (kg/m^2)			26.24 (22.23–30.7)
HbA1c (%)			7 (6.5–7.8)
LDL cholesterol (mg/dL)			102 (84–122)
HDL cholesterol (mg/dL)			50 (41–60)
Triglyceride (mg/dL)			111 (76–183)
eGFR (mL/min/1.73m^2)			67.7 (54.75–81.75)
s-Cr (mg/dL)			0.76 (0.58–0.87)
AST (U/L)			22 (17–28)
ALT (U/L)			23 (16–31)
γGTP (U/L)			28 (18–44)
Diabetes duration (%)		< 10 years	34.1
		≥ 10 years	65.9
Diabetic retinopathy (%)		some	22.2
		none	77.8
Diabetic nephropathy (%)			28.3
Cardiovascular disease (%)			8.5
Stroke (%)			5.1
Peripheral arterial disease (%)			1.7
Treatment for diabetes (%)			
DPP-4 inhibitor			51.2
SGLT-2 inhibitor			42.7
Biguanide			41
GLP-1RA			34.2
Insulin			17.0
Treatment for dyslipidemia (%)			
Statin			59.8
Fibrate			17.1
EPA			8.5
Ezetimibe			25.6

T2D, type 2 diabetes; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium glucose transporter-2; GLP1-RA, glucagon-like peptide-1 receptor agonists; EPA, eicosapentaenoic acid

respectively. A total of 97.4% of patients with type 2 diabetes were receiving antidiabetic treatments, with 59.8% receiving treatment with lipid-lowering drugs. Laboratory data are shown in Table 1. The median interval between the third dose of vaccine and measurement of SARS-CoV-2 spike antibody titers was 72 days (IQR, 61-82).

SARS-CoV-2 spike antibody titers were decreased in obese patients with type 2 diabetes. We examined the association of SARS-CoV-2 antibody titers with age, sex, BMI, HbA1c, and eGFR in patients with type 2 diabetes. The median (25-75th percentile) SARS-CoV-2 antibody titer was 1,262.8 U/mL (286.2-5684.1). SARS-CoV-2 antibody titers were significantly lower in patients with BMI ≥ 25 than those with BMI < 25 (Fig. 1C). However, we observed no significant association of SARS-CoV-2 antibody titers with age, sex, HbA1c, or eGFR (Fig. 1A, B, D and E). Next, we assessed the asso-

ciation of SARS-CoV-2 antibody titers according to the presence or absence of hypertension or dyslipidemia. The results showed that there was no significant difference of SARS-CoV-2 antibody titers between the type 2 diabetics with and those without hypertension or dyslipidemia (Fig. 1F and 1G).

Finally, we investigated the explanatory factors for third-dose vaccine responsiveness in patients with type 2 diabetes. Participants with SARS-CoV-2 antibody titers less than 1,000 U/mL were defined as poor responders. Using multivariable logistic regression analysis, we showed that BMI was the only independent explanatory factor for poor responsiveness after three-dose vaccination in patients with type 2 diabetes (Table 2).

Discussion

In the present study of 112 participants who received three doses of vaccination, obese patients with type 2 diabetes had lower spike IgG antibody titers that non-obese patients with type 2 diabetes.

Obesity is a state of excessive accumulation of adipose tissue, and in obesity, adipocyte hypertrophy, chronic inflammation, and fibrosis occur, leading to adipose tissue dysfunction [8,9]. Obesity has been associated with an increased risk of several bacterial infections, and antibody production in response to vaccine administration is impaired in obesity [10]. Patients with obesity are thus at increased risk of COVID-19, and several factors contributing to the increased sus-

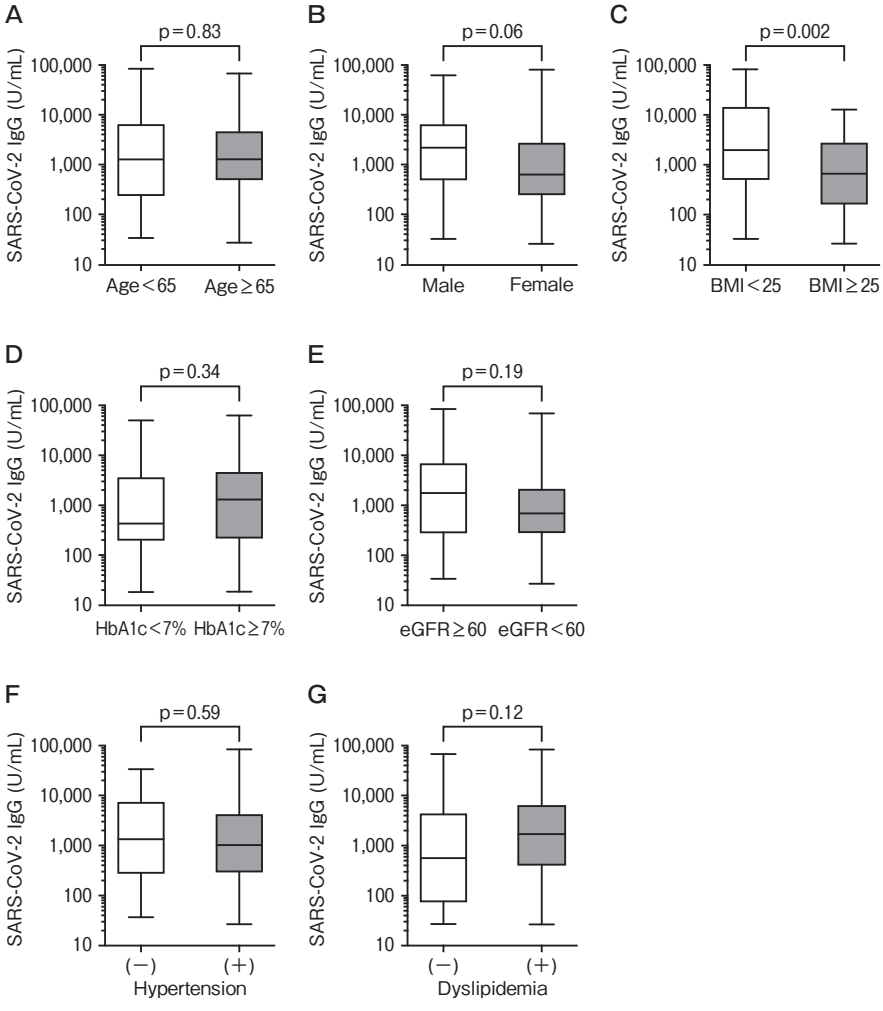

Fig. 1 Anti-SARS-CoV-2 IgG antibody in patients with type 2 diabetes. The solid line in boxes represents the first quartile, the median value, and the third quartile. Mann-Whitney test was performed to compare the two groups.

Table 2 Univariable and multivariable logistic regression analyses for poor responders

	Association with the presence of poor responders (SARS-CoV-2 antibody < 1,000 U/mL)			
	Single		Multiple	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Age (years)	0.97 (0.95–1.02)	0.052	0.99 (0.96–1.02)	0.602
Sex (male)	0.89 (0.42–1.88)	0.757	0.88 (0.37–2.11)	0.782
BMI (kg/m^2)	1.152 (1.07–1.25)	0.001	1.16 (1.06–1.28)	0.001
HbA1c (%)	0.80 (0.56–1.12)	0.192	0.71 (0.46–1.06)	0.101
eGFR (mL/min/1.73m^2)	1.00 (0.98–1.02)	0.974	1.00 (0.98–1.02)	0.957
Hypertension	1.15 (0.53–2.52)	0.709	1.00 (0.39–2.54)	0.995
Dyslipidemia	0.82 (0.38–1.74)	0.605	0.85 (0.35–2.04)	0.722

BMI, body mass index; HbA1c, glycated hemoglobin; OR, odd ratio; CI, confidence interval

ceptibility of patients with obesity have been described [11]. SARS-CoV-2 uses the endosomal or the non-endosomal pathway to enter host cells. In the non-endosomal pathway, the spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), which is expressed in the lung and cardiovascular systems. Transmembrane protease serine 2 (TMPRSS2) activates viral spike proteins, and promotes viral fusion with host cells. In the endosomal pathway, SARS-CoV-2 binds ACE2, but instead of activating TMPRSS2, SARS-CoV-2 is internalized by clathrin-mediated endocytosis. In obesity, hyperinsulinemia has been speculated to increase TMPRSS2 expression via phosphoinositide 3-kinase/protein kinase B/androgen receptor signaling [12-14]. Hyperglycemia increases ACE2 expression, and potentially alters binding of the spike protein to ACE2. Thus, the combination of obesity and type 2 diabetes might exacerbate susceptibility to COVID-19.

Obesity is associated with a reduced immunogenicity in response to vaccination. Fan *et al.* reported that response to hepatitis B vaccines was significantly decreased in an obese population [15]. Yamamoto *et al.* described that higher BMI is associated with lower titers of SARS-CoV-2 spike antibodies in men [16]. Chauvin *et al.* reported that severe obesity accelerates the decline of neutralizing antibodies induced by COVID-19 vaccines [17]. Memory T cells play a critical role in providing long-term immunity. A human cohort study comparing non-obese and obese participants who received influenza vaccine showed that obese participants had reduced memory T cell activation [18]. The mechanisms by which obesity reduces vaccine efficacy include shortened T cell telomeres and increased expression of PD-1 and PD-L1, which induce memory T cells exhaustion and reduce memory T cells responsiveness [19-21]. B cells also play a critical role in providing long-term immunity. The humoral B cell response produces SARS-CoV-2 virus-specific antibodies in the blood. After recovery from COVID-19, class-switched IgG and IgM memory B cells specific for SARS-CoV-2 are recognized, but over time, the proportion of class-switched IgM memory B cells decreases and class-switched IgG memory B cells become the dominant population [22]. Several studies indicate that memory B cell responsiveness is reduced in obesity. The mechanisms by which obesity reduces vaccine efficacy include shortened B cell telomeres and hyperleptinemia-induced downregulation of activation-induced cytidine deaminase (AID)—which is essential for class switch recombination, somatic hypermutation and IgG production—and its transcriptional regulator E47 [23]. For these reasons, obese individuals may have reduced antibody production against SARS-CoV-2 and may be more susceptible to infection despite COVID-19 vaccination.

Previous reports have shown that type 2 diabetic patients using GLP-1 receptor agonists or DPP-4 inhibitors have a reduced mortality rate of COVID-19. This phenomenon is assumed to involve not only the glycose-lowering effects but also the anti-inflammatory, immunomodulatory, antifibrotic, antithrombotic, and vascular endothelial protective actions of GLP-1 receptor agonists and DPP-4 inhibitors; however, the detailed mechanisms are not clear [24]. In this study, SARS-CoV-2 antibody titers were also examined in relation to the presence or absence of DPP-4 inhibitors,

SGLT2 inhibitors, GLP-1 receptor agonists, biguanides, and insulin, but no associations were found between any of these agents and SARS-CoV-2 antibody titers (data not shown). Furthermore, when the presence or absence of DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, biguanides, and insulin were added as explanatory variables in the multivariable logistic regression analysis, none of the drugs was a factor affecting SARS-CoV-2 antibody titers variation (data not shown).

Despite its potentially useful findings, this study has several limitations. First, due to its cross-sectional design this study could not define a causal relationship between the antibody titers and BMI in patients with type 2 diabetes. Whether SARS-CoV-2 spike antibodies are effective in preventing infection or severe disease has not been studied, and prospective studies will be needed to answer this question. Second, the history of COVID-19 infection was self-reported, and asymptomatic infected patients could not be excluded, which may have influenced our results. Third, some patients were taking multiple diabetes medications, and the effects of different medications have not been adequately studied. Some diabetic drugs may affect the infectivity and severity of COVID-19 and require further study. Finally, anti-SARS-CoV-2 spike IgG measurements were taken on the day of the regular clinic visit, so there was a 2-3 months variation among patients in the interval between the third dose of vaccine and measurement of the SARS-CoV-2 spike antibody titers. A further investigation using a standardized period between vaccination and antibody measurement would be warranted.

In summary, we report an association between the anti-SARS-CoV-2 spike IgG antibody titer after three doses of vaccination and BMI in patients with type 2 diabetes. Our study suggests that vaccine efficacy may be attenuated in obese patients with type 2 diabetes, and such patients may require additional vaccination or even continuous infection control. Elucidation of the mechanism underlying this phenomenon remains for a future study.

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