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ORIGINAL CONTRIBUTIONS

Antibody Response to SARS-CoV-2 Vaccines in People with Severe Obesity

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Abstract

Aim Obesity is a disease complicating the course of COVID-19 and SARS-CoV-2 vaccine effectiveness in adults with obesity may be compromised. Our aim is to investigate the spike-protein receptor-binding domain antibody titers against BNT162b2 mRNA and inactivated SARS-CoV-2 (CoronaVac) vaccines in people with severe obesity. It is anticipated that the results to be obtained may provide invaluable information about future SARS-CoV-2 vaccination strategies in this vulnerable population.

Methods A total of 124 consecutive patients with severe obesity (age > 18 years, BMI ≥ 40 kg/m^2) presenting between August and November 2021 were enrolled. The normal weight control group (age > 18, BMI 18.5–24.9 kg/m^2) was recruited from 166 subjects who visited the vaccination unit. SARS-CoV-2 spike-protein antibody titers were measured in patients with severe obesity and in normal weight controls who received two doses of BNT162b2, or CoronaVac vaccines. SARS-CoV-2 IgG Nucleocapsid Protein antibody (NCP Ab) testing was performed to discover prior SARS-CoV-2 infection. Blood samples were taken from individuals at 4th week and after 2nd dose of vaccination. SARS-CoV-2 IgG antibody titers were determined by quantitative serological methods.

Results A total of 290 individuals (220 female, 70 male) who have received two doses of BNT162b2 or CoronaVac vaccines were enrolled in the study. Seventy had prior SARS-CoV-2 infection. In 220 subjects (non-prior infection) vaccinated with BNT162b2 or CoronaVac, the antibody titers against SARS-CoV-2 spike antigen of patients with severe obesity were significantly lower than normal weight controls ($p = 0.001$, $p = 0.001$ respectively). In seventy subjects with prior SARS-CoV-2 infection, spike antigen antibody titers in patients with severe obesity, vaccinated with BNT162b2 or CoronaVac, were not significantly different from normal weight controls ($p = 0.1$, $p = 0.1$ respectively). In patients with severe obesity, with and without prior SARS-CoV-2 infection, spike antigen antibody levels of those vaccinated with BNT162b2 were found to be significantly higher than those vaccinated with CoronaVac ($p = 0.043$, $p < 0.001$ respectively).

Conclusion Patients with severe obesity generated significantly reduced antibody titers against SARS-CoV-2 spike antigen after CoronaVac and BNT162b2 vaccines compared to people with normal weight. Antibody levels in patients with severe obesity vaccinated with BNT162b2 were found to be significantly higher than those vaccinated with CoronaVac. People living with severe obesity should be prioritized for COVID-19 vaccination and BNT162b2 vaccine may be recommended for this vulnerable population.

Keywords Severe obesity · Vaccines · Antibody response

Key Points
- Individuals with severe obesity had low antibody responses to the BNT163b2 vaccine.
- Individuals with severe obesity had low antibody responses to the CoronaVac vaccine.
- BNT162b2 vaccine responses were better than CoronaVac in severely obese individuals.
- BNT162b2 can be recommended for the COVID-19 vaccine to this susceptible population.

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Introduction

Coronavirus disease 2019 (COVID-19) led to a devastating epidemic in late 2019 and remains to be the cause for high morbidity and mortality worldwide [1, 2]. 408,910,752 confirmed global cases of SARS-CoV-2 infection were reported as of February 15, 2022, of which 5,802,226 resulted in death [3]. A total of 12,051,852 people were infected in this period in Turkey, and 88,312 died [4]. Amidst the

COVID-19 pandemic, several promising vaccines were developed and more than 10 billion doses of COVID-19 vaccine have been administered so far in the world [5]. Inactivated whole virus, lipid nanoparticle encapsulated mRNA, adenovirus vectored, and protein subunit vaccines are among those discovered [6]. In severe obesity, where inflammatory response is exaggerated, the risk of acute respiratory distress syndrome is increased, and the associated mortality rate was found to be approximately 2% [7]. Our aim is to investigate the spike-protein receptor-binding domain antibody titers against BNT162b2 mRNA and inactivated severe adult respiratory syndrome coronavirus 2 (SARS-CoV-2) (CoronaVac) vaccines in people with severe obesity.

Material and Method

Patient Selection

In total, 124 consecutive patients (age > 18 years; body mass index (BMI) ≥ 40 kg/m^2) with severe obesity who visited between August and November 2021 were invited to the study. Normal weight control group was recruited from subjects who visited the vaccination unit during the same period. SARS-CoV-2 IgG Nuclear Capsid Protein (NCP) Antibody Test was administered to all subjects to discover those who had prior SARS-CoV-2 infection. The study group (BMI ≥ 40 kg/m^2, $n = 124$) and normal weight control group (BMI 18.5–24.9 kg/m^2, $n = 166$) have already received two doses of CoronaVac or BNT162b2 vaccines. In the group with no prior infection, 69 patients with severe obesity and thirty-one normal-weight individuals received two doses of BNT162b2 vaccine; thirty-four with severe obesity and 86 normal-weight individuals received two doses of CoronaVac vaccine. Among seventy patients who had prior infection, eleven with severe obesity and nineteen with normal-weight individuals received two doses BNT162b2 vaccine; ten with severe obesity and thirty normal-weight individuals received two doses of CoronaVac vaccine.

Data Collection

Patients' weight, height, sex, age, and clinical characteristics such as presence of type 2 diabetes (T2DM) and hypertension (HT), fasting blood glucose (FBG), and glycosylated hemoglobin A1c (HbA1c) values were recorded. Peripheral blood samples were obtained 28 days after the last dose from adults who had BNT162b2 or inactive CoronaVac vaccines. Samples were studied at Medical Microbiology Laboratory, Serology Unit. Prior SARS-CoV-2 infection was determined by mCLIA-principle SARS-CoV-2 IgG NCP (Abbott, IL, USA) test in the Architect i1000 (Abbott, IL, USA) closed fully automated system. IgG antibody responses specific to Receptor Binding Domain (RBD) region of the virus were quantitatively determined.

SARS-CoV-2 IgG NCP Antibody Test

Approximately 3 mL of blood taken from volunteers participating in the study into tubes containing vacuum separator gel was centrifuged at 5000 rpm for 5 min, and serum obtained was transferred to microcentrifuge tubes and stored at − 20 °C until the study day. On the day of the test, serum samples were first brought to + 4 °C, then to room temperature (+ 18 °C, + 25 °C) and made ready for use. The SARS-CoV-2 IgG test (ARCHITECT IgG test, Abbott, USA), which semi-quantitatively detects IgG antibodies against the Nucleocapsid (NCP) protein of SARS-CoV-2, using the chemiluminescent microparticle immunoassay (CMIA) method, was performed. The results obtained from all sera studied were given as Index (S/C) units [8].

In a previous study conducted in our microbiology laboratory at Cerrahpaşa Medical Faculty in order to determine the diagnostic performance of antibody tests, the mean NCP IgG (2.03 S/Co) in the acute period of COVID-19 was considered as the cut-off index [8]. Those with a concentration above 2.03 S/Co were considered to have previously contacted SARS-CoV-2 and concentrations between 1.4 and 2.03 S/Co were labeled as inactive vaccine-induced [9].

SARS-CoV-2 IgG II Quant Antibody Test

SARS-CoV-2 IgG test can quantitatively detect immunoglobulin class G (IgG) antibodies, including neutralizing antibodies against the receptor binding region (RBD) of the spike protein S1 subunit of SARS-CoV-2, using the chemiluminescent microparticle immunoassay (CMIA) method (ARCHITECT IgG II Quant test, Abbott, USA). The results obtained from all serums studied were evaluated as arbitrary unit/mL (AU/mL). The concentrations obtained in AU/mL were multiplied by the correlation coefficient of 0.142 and converted to the "Binding Antibody Unit (BAU/mL)" in World Health Organization's International Standard on Anti-SARS-CoV-2 immunoglobulin [8]. Concentrations of 50 AU/mL or 7.1 BAU/mL and above were considered positive accordingly. Moreover, it was reported that this test was 100% compatible with the plaque reduction neutralization test (PRNT), and a concentration of 1050 AU/mL was associated with a 1:80 dilution of PRNT [10].

Exclusion Criteria

Patients with a diagnosis of immunodeficiency disorders, oncological and hematological malignancies receiving chemotherapy and/or immunotherapy, pregnant women,

individuals under 18 years of age, and with BMI < 18.5 kg/m^2 were not included in the study.

Statistics

SPSS 20 program was used to compare data. After the normal distribution was determined, data showing normal distribution was acquired using independent sample *t* test, and comparison of data, not showing normal distribution, was done with Mann–Whitney *U* test. Pearson and Spearman tests were used for correlation according to the distribution of the data. The one-way ANOVA test was used to compare non-normally distributed data. Results were evaluated at a 95% confidence interval, and $p < 0.05$ was considered statistically significant. Required sample size was calculated as 176 for 2-tailed *t* test with 5% significance level to achieve 95% power.

Results

Seventy subjects were found to have prior infection after being evaluated with the SARS-CoV-2 IgG NCP Antibody Test. In 100 patients vaccinated with BNT162b2 who had no prior infection, antibody titers against SARS-CoV-2 spike antigen of individuals with BMI ≥ 40 kg/m^2 ($n = 69$) were significantly lower than those with BMI 18.5–24.9 kg/m^2 ($n = 31$) ($p = 0.001$) (Table 1). In 120 patients vaccinated with CoronaVac who had no prior infection, antibody titers against SARS-CoV-2 spike antigen of individuals with BMI ≥ 40 kg/m^2 ($n = 34$) were significantly lower than those with BMI 18.5–24.9 kg/m^2 ($n = 86$) (p: 0.001) (Table 2). Among subjects with prior infection, the antibody titers in people vaccinated with BNT162b2 BMI ≥ 40 kg/m^2 ($n = 11$) were similar to those with BMI 18.5–24.9 kg/m^2 ($n = 19$) ($p = 0.1$) (Table 1) and in subjects vaccinated with CoronaVac BMI ≥ 40 kg/m^2 ($n = 10$) were similar to those with BMI 18.5–25.0 kg/ m^2 ($n = 30$) ($p = 0.1$) (Table 2).

In patients with severe obesity, without and with prior SARS-CoV-2 infection, SARS-CoV-IgG levels of those vaccinated with BNT162b2 were found to be significantly higher than those vaccinated with CoronaVac ($p < 0.001$, $p = 0.043$ respectively) (Table 3).

In normal weight individuals without prior infection, SARS-CoV-IgG level was significantly higher after BNT162b2 vaccine ($n = 31$) than CoronaVac ($n = 86$) ($p < 0.001$). In normal weight individuals with prior infection, SARS-CoV-IgG level was significantly higher after BNT162b2 vaccine ($n = 19$) than in individuals who received CoronaVac ($n = 30$) ($p = 0.007$).

The correlation analysis in the non-prior infection study arm (in patients with severe obesity and normal weight controls) demonstrated that age ($p = 0.018$, $r = -0.211$) and BMI ($p = 0.008$, r: -0.237) were inversely correlated with SARS-CoV-IgG titers in individuals vaccinated with BNT162b2; age ($p = < 0.001$, $r = -0.415$), BMI ($p = < 0.001$, $r = -0.431$), T2DM ($p = 0.007$, $r = -0.232$), and HT ($p = < 0.001$, r: -0.429) were inversely correlated

Table 1 Clinical and laboratory characteristics of BNT162b2-vaccinated group

	Non-prior infection $n = 100$ (76%)			Prior infection $n = 30$ (24%)		
	Severe obesity $n = 69$ (69%)	Normal weight $n = 31$ (31%)	p	Severe obesity $n = 11$ (36%)	Normal weight $n = 19$ (64%)	p
Age	42 ± 10	39 ± 10	0.06	45 ± 9	47 ± 17	0.1
Sex (F/M)	58/11 (84%/16%)	16/15 (51%/49%)	0.001	6/5 (54%/46%)	11/8 (57%/43%)	0.8
BMI	43.2 ± 4.5	22.9 ± 2	< 0.001	45.8 ± 5.2	21.8 ± 1.7	< 0.001
T2DM	24 (34%)	2 (6%)	< 0.001	1 (9%)	4 (21%)	0.6
HT	8 (25%)	0	< 0.001	2 (18%)	0	0.1
FPG (mg/dL)	129 ± 49	88 ± 35	0.004	103 ± 22	104 ± 41	0.2
HbA1c %	7.3 ± 1.7	5.5 ± 0.8	< 0.001	6 ± 0.6	5.9 ± 0.8	0.2
SARS-CoV-2IgG* AU/mL	5823 (1883–16,094)	19,371 (8409–28,791)	< 0.001	39,043 (8808–40,000)	14,115 (7221–24,663)	0.1
SARS-CoV-2IgG€ AU/mL	*4914 ± 4.4*	*14,764 ± 1.8*	*< 0.001*	*14,764 ± 3.6*	*13,359 ± 1.8*	*0.1*

F female, *M* male, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *FPG* fasting plasma glucose, *HbA1c* glycosylated hemoglobin A1c, *HT* hypertension, *SARS-CoV-IgG (AU/mL)* severe acute respiratory syndrome-coronavirus-immunoglobulin G (arbitrary units per milliliter)

Severe obesity: BMI ≥ 40 kg/m^2, normal weight: BMI 18.5–24.9 kg/m.^{2}

*Since the data were not normally distributed, the median (ınterquantile range 25–75%) value was given

€Geometric mean values are given

$p < 0.05$ suggested statistical significance

Table 2 Clinical and laboratory characteristics of the CoronaVac-vaccinated group

	Non-prior infection $n=120$ (75%)			Prior infection $n=40$ (25%)		
	Severe obesity $n=34$ (28%)	Normal weight $n=86$ (72%)	p	Severe obesity $n=10$ (25%)	Normal weight $n=30$ (75%)	p
Age	63 ± 11	39 ± 11	< 0.001	62 ± 9	42 ± 11	< 0.001
Sex (F/M)	32/2 (94%/6%)	70/16 (81%/19%)	0.1	8/2 (80%/20%)	19/11 (63%/37%)	0.4
BMI	43 ± 4	23 ± 2	0.01	44 ± 5	23 ± 3	< 0.001
T2DM	18 (52%)	5 (5%)	< 0.001	5 (50%)	12 (40%)	0.6
HT	18 (52%)	2 (2%)	< 0.001	4 (40%)	2 (6%)	0.2
FPG (mg/dL)	101 ± 41	88 ± 14	0.3	96 ± 18	114 ± 38	0.3
HbA1c %	5.8 ± 2.6	5.6 ± 0.8	0.1	6.3 ± 1.1	6.6 ± 1.5	0.6
SARS-CoV-2 IgG* AU/mL	178 (13–554)	4894 (2776–7656)	< 0.001	3221 (1741–20,243)	7060 (4317–14,005)	0.1
SARS-CoV-2 IgG€ AU/mL	*221 ± 5.4*	*4914 ± 2.2*	*< 0.001*	*2980 ± 9*	*6634 ± 2.4*	*0.1*

F female, *M* male, *BMI* body mass index, *T2DM* type 2 diabetes mellitus, *FPG* fasting plasma glucose, *HbA1c* glycosylated hemoglobin A1c, *HT* hypertension, *SARS-CoV-IgG (AU/mL)* severe acute respiratory syndrome-coronavirus-immunoglobulin G (arbitrary units per milliliter)

Severe obesity: BMI ≥ 40 kg/m^2, normal weight: BMI 18.5–24.9 kg/m.^{2}

*Since the data were not normally distributed, the median (ınterquantile range 25–75%) value was given

€Geometric mean values are given

$p < 0.05$ suggested statistical significance

with SARS-CoV-2 IgG titers in individuals vaccinated with CoronaVac.

Sex Comparison

SARS-CoV-2 Ig G levels were found to be higher in males than females only in normal-weight individuals vaccinated with BNT162b2 in the non-prior infection arm ($p=0.02$). Otherwise, in the rest of the study groups, there was not any significant difference in SARS-CoV-2 IgG levels between men and women when we evaluated patients with severe obesity and normal weight individuals who received BNT162b2 or Coronavac vaccine.

Discussion

In our study, we found that spike antigen antibody responses against BNT162b2 and CoronaVac vaccines were significantly lower in patients with severe obesity compared to those with normal weight and the antibody response against BNT162b2 vaccine in patients with severe obesity was significantly greater than CoronaVac.

In people with severe obesity chronic inflammation, which develops as a result of dysfunctional adipose tissue, negatively affects T cell functions, antibody response, and macrophage migration. Therefore, one can hypothesize that immune dysfunction increases the risk of SARS-CoV-2 infection and decreases vaccine responses in individuals with severe obesity [11–15]. In a recent COVID-19 vaccine study by Pellini et al., while age and gender were found to be associated with antibody response, BMI and HT were not found to be related [16]. Watanabe et al. concluded that BMI is inversely correlated with humoral and cell-mediated immune response, obesity is associated with a reduced adaptive response to a COVID-19 mRNA vaccine, and weight loss and metabolic improvement may reverse this effect [17]. In our study, in the non-prior infection arm (in patients with severe obesity and normal weight controls), BMI and age were negatively correlated with SARS-CoV-2 IgG levels in both CoronaVac- and BNT162b2-vaccinated individuals; T2DM, HT, and SARS-CoV-2 IgG levels were found to be inversely correlated in people who received CoronaVac vaccine.

It is excessive visceral adipose tissue that causes chronic inflammation that impairs immune system and thus antibody development [18]. Malavazos et al. have shown that antibody titers of individuals with abdominal obesity were found to be lower than those without [19]. BMI is a limited measure in distinguishing between visceral (proinflammatory) and subcutaneous (protective) adipose tissue [19]. Moreover, the magnitude and durability of antibody response to mRNA-based vaccines are not affected by BMI [20]. The patients in our study group had severe obesity (BMI ≥ 40 kg/m^2) and it is accepted that individuals with a BMI of 35 and above are more likely to have abdominal obesity [21]. In this case, it may be the increased waist

Table 3 SARS-CoV-2 IgG levels in patients with severe obesity

	Non-prior infection n = 220 (75%)					*Prior infection n = 70 (25%)*				
	SARS-CoV-IgG response*					*SARS-CoV-IgG* response*				
	BNT162b2	*n*	CoronaVac	*n*	*p*	BNT162b2	*n*	CoronaVac	*n*	*p*
	n = 100 (45%)		*n* = 120 (55%)			*n* = 30 (42%)		*n* = 40 (58%)		
Severe obesity[*]	5823 (1883–16,941)	*69 (69%)*	178 (13–554)	*34 (28%)*	*< 0.001*	39,043 (8808–40,000)	*11 (36%)*	3221 (1741–20,243)	*10 (25%)*	0.043
	€4914 ± 4.4		*221 ± 5.4*		*< 0.001*	*14,764 ± 3.6*		*2980 ± 9*		*0.043*
Normal weight[*]	19,371 (8409–28,791)	*31 (31%)*	4894 (2776–7656)	*86 (72%)*	*< 0.001*	14,115 (7221–24,663)	*19 (64%)*	7060 (4317–14,005)	30 (75%)	< 0.007
	€14,764 ± 1.8		*4447 ± 2.2*		*< 0.001*	*13,359 ± 1.8*		*6634 ± 2.4*		*< 0.007*

SARS-CoV-IgG (AU/mL), severe acute respiratory syndrome-coronavirus-immunoglobulin G (arbitrary units per milliliter)

Severe obesity: BMI ≥ 40 kg/m^2, normal weight: BMI 18.5–24.9 kg/m.^{2}

[*]Since the data were not normally distributed, the median (interquantile range 25–75%) value was given

[€]Geometric mean values are given

$p < 0.05$ suggested statistical significance

circumference not BMI, depicting a negative correlation with antibody response in our patients with severe obesity.

In a study comparing CoronaVac and BNT162b2 vaccine responses in the general population, Mok et al. evaluated the antibody levels of patients who received BNT162b2 and CoronaVac vaccines. Better humoral response was obtained in the BNT162b2 vaccine-administered arm [17]. In our study, the antibody responses of groups with normal weight and severe obesity, with non-prior and prior infection, were evaluated separately. Subjects who received BNT162b2 vaccine had a more powerful immune response in all groups.

A study reported from Hong Kong, two doses of BNT162b2 vaccine revealed significantly higher levels of PRNT50, PRNT90, surrogate virus neutralization test (sVNT), spike receptor binding, spike N-terminal domain binding, spike S2 domain binding, spike Fc receptor (FcR) binding, and antibody avidity compared to CoronaVac vaccine [22]. In another study, it was reported that while one dose of BNT162b2 vaccine is sufficient for SARS-CoV-2-naive individuals to generate a strong neutralizing antibody reaction, two doses of CoronaVac vaccine were required for a similar response [23]. In a surveillance study examining IgG seropositivity after two different vaccinations in 56,261 individuals in Chile, IgG positivity after the first dose of CoronaVac was found to be 29%, while it reached 77% in 3 weeks after the second dose and decreased thereafter. On the other hand, while IgG positivity was greater than 70% after the first dose of BNT162b2, it was found to be higher (> 96%) 3 weeks after the second dose and remained above 92% until the end of 20 weeks [24]. This in part may be explained by BNT162b2 vaccine inducing the production of interferon proteins, possibly with innate immune system activation by the combined action of mRNA and lipids [25].

Data from Chile demonstrated that Coronavac vaccine was highly effective in protecting against severe disease and death on a two dose shedule 28 days apart [26]. On the other hand, BNT162b2 vaccine was found to be more effective only after the first dose of vaccination [27]. In a retrospective study conducted with patients who previously had COVID-19, no difference was found between the effectiveness of a single or two doses of BNT162b2 vaccine. In the same study, it was stated that patients with prior SARS-CoV-2 infection could be protected with a single dose of BNT162b2 vaccine [28]. Moreover, in a preclinical study, it was demonstrated that BNT162b2 vaccination elicits a potent SARS-CoV-2 RBD-specific B cell memory response resembling natural infection [29]. In our study, we found that antibody responses obtained with BNT162b2 vaccine in normal weight and severely obese individuals either with or without prior infection were found to be significantly higher than in individuals who received CoronaVac vaccine.

Wheeler et al. did not find a significant difference in antibody titers between sexes in their study with healthy

individuals who were administered BNT162b2 vaccine [30]. In our study, SARS-CoV-2 Ig G levels were found to be higher in males than females only in normal-weight individuals vaccinated with BNT162b2 in the non-prior infection arm ($p = 0.02$). Otherwise, there was not any significant difference in SARS-CoV-2 IgG levels between men and women in the rest of the study groups.

Limitations

A clear cut interpretation would have been made regarding the protection status of vaccines in patients with severe obesity compared to normal weight controls if the protective neutralizing antibody titers were known. Waist circumference measurement values or HOMA-IR results were not included in our study. The antibody levels of the patients were not checked before the vaccine was administered.

Conclusion

Patients with severe obesity generated significantly reduced antibody titers against SARS-CoV-2 spike antigen after CoronaVac and BNT162b2 vaccines compared to people with normal weight. Antibody levels in patients with severe obesity vaccinated with BNT162b2 were found to be significantly higher than those vaccinated with CoronaVac. People living with severe obesity should be prioritized for COVID-19 vaccination and BNT162b2 vaccine may be recommended for this vulnerable population until more robust evidence is obtained to direct future vaccination strategies.

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Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

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