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Risk Factors Influencing Seroconversion after Inactive SARS-CoV-2 Vaccination in People Living with Obesity

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Keywords
Obesity · Vaccination · Antibody response

Abstract

Introduction: The aim of this study was to investigate the antibody titers against SARS-CoV-2 spike antigens and the risk factors affecting antibody levels in people living with obesity (PwO) after inactive SARS-CoV-2 vaccine (CoronaVac) administration. ***Methods:*** 169 consecutive patients with obesity who visited the Center for Obesity Management at Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Hospitals, between May and August 2021, were invited to the study. The nonobese control group was recruited from 191 subjects who visited the Cerrahpaşa Hospitals Vaccination Unit. The study group and the nonobese control group have already received two doses of inactive SARS-CoV-2 vaccine. The SARS-CoV-2 IgG nucleocapsid antibody test was administered to patients and control subjects to discover those who had prior SARS-CoV-2 infection. Forty-one patients who had prior infection and received two doses of vaccine were also included in the study as a subgroup. Blood samples were taken on the 3rd to 4th week after the second vaccination. SARS-CoV-2 IgG antibody titers were determined by quantitative serological methods. ***Results:*** Antibody titers against SARS-CoV-2 spike antigen of individuals with BMI ≥30.0 kg/m^2 were significantly lower than those with BMI <30 kg/m^2 ($p = 0.001$) in the study group. Moreover, the antibody titers in people with BMI ≥30.0 kg/m^2 were significantly lower than in those having a BMI <30.0 kg/m^2 in the subgroup ($p = 0.03$). Age ($p = 0.03$), BMI ($p = 0.006$), and hypertension ($p = 0.03$) were found to be independent risk factors for antibody response in PwO. Women with non-prior SARS-CoV-2 infection showed a significantly higher antibody response then men ($p = 0.001$). ***Conclusion:*** SARS-CoV-2-Immunoglobulin G antibody levels against inactive (CoronaVac) vaccine were found to be lower in PwO compared to nonobese individuals. Antibody titers may be measured, and booster doses should be delivered accordingly in PwO for optimal protection.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, which emerged in Wuhan, China, at the end of 2019, spread to the whole world in a short time and caused a pandemic [1]. CO-

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VID-19 was first reported to the World Health Organization (WHO) on the December 31, 2019, and on March 11, 2020, the WHO declared the COVID-19 pandemic [2].

As of November 28, 2021, 194 vaccines were in preclinical and 132 vaccines in clinical stages of development, 7 of which have been approved for emergency use [3]. The vaccines for emergency use are: Comirnaty (Pfizer/BioNTech), AZD1222/ChAdOx1 (AstraZeneca/Oxford University), Ad26.COV2.S (Johnsson&Johnsson/Janssen), CoronaVac AKO domain (Sinovac Life Sciences), mRNA-1273 (Moderna/NIAID), Sputnik V (Gamaleya Research Institute), and BBV152/Covaxin (Bharat Biotech) [3].

CoronaVac, an inactivated virus vaccine, manufactured by Sinovac Life Sciences (Beijing, China), was the first vaccine to be administered in Turkey in line with the recommendations of the Ministry of Health. This vaccine received emergency use approval from the Turkish Medicines and Medical Devices Agency after a 14-day safety test [4]. As a result of this emergency use approval, CoronaVac vaccine was administered to health care professionals followed by public in risk [4]. The CoronaVac vaccine is administered in two doses according to the manufacturer's instructions. In our country, this dose interval has been determined as 28 days. As of November 28, 2021, a total of 120,100,914 vaccines have been administered in Turkey so far [4].

Obesity, a chronic, relapsing, multifactorial disease, is now shown as the second most important cause of preventable death after smoking. Obesity develops with excessive fat accumulation in the body due to genetic, epigenetic, environmental, biologic, behavioral, and sociocultural factors. According to the WHO, it is estimated that there were over 650 million people living with obesity (PwO) worldwide in 2016 [5]. The WHO reported 16 million PwO in Turkey in 2016, placing Turkey among those countries with the highest prevalences in Europe [6].

Obesity negatively affects the immune system function and host defense mechanisms. It creates an inflammatory condition associated with chronic activation of the immune system, enabling infectious diseases to become more common and vaccine failure to be higher [7]. In addition, altered pulmonary physiology, increased receptors for virus spread, increased viral diversity, and titers all together complicate SARS-CoV-2 infection in obesity [7]. In this study, we evaluated the antibody titers against SARS-CoV-2 spike antigen and the risk factors affecting these antibody levels in PwO.

Materials and Methods

Patient Selection

Our work makes use of a cross-sectional data set with different groups. 169 consecutive patients (age >18 years) with obesity who visited the Center for Obesity Management at Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Hospitals, between May and August 2021, were invited to the study. The nonobese control group was recruited from the subjects who visited the Cerrahpaşa Hospitals Vaccination Unit during the same time period. Those enrolled in the study were grouped in alignment with the obesity classification citeria of the WHO [5]. SARS-CoV-2 IgG nucleocapsid protein (NCP) antibody test was administered to patients and control subjects to discover those who had prior COVID-19. The study group (body mass index [BMI] ≥30 kg/m^2, n = 128) and the nonobese control group (BMI <30 kg/m^2, n = 147) have already received two doses of inactivated SARS-CoV-2 vaccine. Forty-one patients who had prior COVID-19 and received two doses of vaccine were included in the study as a subgroup. Forty-four who had prior COVID-19 detected in the nonobese subjects became controls for this subgroup.

Data Collection

Weight in kilograms and height in meters, sex, age, and clinical characteristics of the patients were recorded. Blood samples were taken on the 3rd to 4th week after the second vaccination. SARS-CoV-2 IgG antibody titers were determined by quantitative serological methods.

Exclusion Criteria

Patients with a diagnosis of immunodeficiency disorders, oncological and hematological malignancies receiving corticosteroid, chemotherapy and/or immunotherapy, pregnant women, and individuals under 18 years of age were not included in the study.

SARS-CoV-2 IgG NCP Antibody Test

Approximately 3 mL of blood taken from the volunteers participating in the study into tubes containing vacuum separator gel was centrifuged at 5,000 rpm for 5 min, and the serum obtained was transferred to microcentrifuge tubes and stored at −20°C for two to 3 weeks. On the day of the test, serum samples were first brought to +4°C and 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 semiquantitatively detects IgG antibodies against the NCP of SARS-CoV-2, using the chemiluminescent microparticle immunoassay method was used. The results obtained from all sera studied were given as index specimen/calibrator (S/C) units (strength of response in relative light units reflects quantity of IgG present and is compared to a calibrator to determine the calculated index S/C for a sample) and were evaluated as <1.4 S/C negative and ≥1.4 S/C positive [8].

SARS-CoV-2 IgG II Quant Antibody Test

In the study, the SARS-CoV-2 IgG test was performed, which can quantitatively detect immunoglobulin class G (IgG) antibodies, including neutralizing antibodies against the receptor-binding region of the spike protein S1 subunit of SARS-CoV-2, using the chemiluminescent microparticle immunoassay method (ARCHITECT IgG II Quant test, Abbott, USA). The results obtained from

Table 1. Demographic, clinical characteristics, and antibody titers of the different study groups

	BMI <30 (n = 147)	BMI ≥30 (n = 128)	p value
Demographic, clinical characteristics, and antibody titers of the study group (non-prior infection)			
Age, years	52±18	58±13	<0.001
Sex (F/M)	95/52	84/44	0.7
BMI	24±2	35±4	<0.001
Type 2 DM	3.4% (5)	38% (49)	<0.001
Duration, years	8±1	15±6.6	0.065
HbA1c, %	7.6±1	7±1	0.3
HT	3.4% (5)	30% (39)	<0.001
Seroconversion rate, %	99.4	83.5	<0.001
SARS-CoV-IgG, AU/mL	2,350 (385–5,821)	242 (105–479)	<0.001
	BMI <30 (n = 44)	BMI ≥30 (n = 41)	p value
Demographic, clinical characteristics, and antibody titers of the subgroup (prior infection)			
Age, years	51±17	59±12	<0.001
Sex (F/M)	28/16	29/12	0.4
BMI	24±3	35±5	<0.001
Type 2 DM	4.5% (2)	36% (15)	<0.001
HT	2.3% (1)	9.8% (4)	0.1
SARS-Co-V-IgG (AU/mL)*	4,600 (1,853–9,540)	2,733 (1,477–4,920)	0.03
	Prior infection (n = 85)	Non-prior infection (n = 275)	p value
Demographic, clinical characteristics, and antibody titers of patients with prior and non-prior SARS-CoV-2 infection			
Age, years	57±15	57±16	0.7
Sex (F/M)	57/28	179/96	0.7
BMI	29±6	29±6	0.7
Type 2 DM	20% (17)	19% (54)	0.6
HT	5% (5)	16% (44)	0.02
SARS-CoV-2, AU/mL	3,395 (1,615–7,739)	478 (206–2,709)	<0.001

BMI, body mass index; DM, diabetes mellitus; HT, hypertension; SARS-CoV-IgG (AU/mL), severe acute respiratory syndrome-coronavirus-immunoglobulin G (arbitrary units per milliliter). * Since the data were not normally distributed, the median (interquartile range 25%–75%) value was given.

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 the WHO's International Standard [1] on anti-SARS-CoV-2 immunoglobulin. Accordingly, concentrations of 50 AU/mL or 7.1 BAU/mL and above were considered positive. In addition, it was reported that this test was 100% compatible with the plaque reduction neutralization test (PRNT), and a concentration of 1,050 AU/mL was associated with a 1:80 dilution of PRNT [9].

Statistics

The SPSS 20 program was used to compare the data. After the normal distribution was determined, data showing normal distribution were acquired using independent sample t test, and the comparison of the data not showing normal distribution was done with the Mann-Whitney U test. Pearson and Spearman tests were used for correlation according to the distribution of the data. We found that the data were non-normally distributed with the Kruskal-Wallis test. The non-normally distributed module of the one-way ANOVA test (Tamhane's T2) was used to compare non-normally distributed data. When SARS-CoV-2 antibody levels, age, BMI, sex, the presence of DM, and HT were tested for normality; antibody levels were found to be non-normally distributed. Linear regression analysis was used for independent factor detection. In the linear regression analysis, the SARS-CoV-2 level was taken as the dependent variable and age, sex, BMI, HT, and type 2 DM as independent variables. In the data, SARS-CoV-2 antibody levels, age, and BMI were taken as continuous variables and type 2 DM, HT, and sex were taken as categorical variables. The results were evaluated at a 95 per cent confidence interval, and $p < 0.05$ was considered statistically significant.

Sample Size

Required sample size was calculated as 74 for 2-tailed t test with 5% significance level to achieve 95% power.

Table 2. Comparison among different BMI groups (non-prior infection)

	Group 1 BMI: 18.5–24.9 (n = 78)	Group 2 BMI: 25.0–29.9 (n = 69)	Group 3 BMI ≥30.0 (n = 128)
Age, years	46±18	58±16	62±12
Sex (F/M)	24/54	28/41	44/84
BMI	22±1.6	27±1.2	35±4.8
Type 2 DM, *n* (%)	2 (2)	3 (4)	49 (38)
HT, *n* (%)	3 (3)	2 (2)	39 (30)
SARS-CoV*	3,427 (789–6,712)	672 (305–3,295)	126 (109–484)

SARS-CoV-2 (AU/mL): group 1; group 2 (p = 0.01), group 2; group 3 (p < 0.001), group 1; group 3 (p < 0.001). Age: group 1; group 2 (p < 0.001), group 2; group 3 (p = 0.1), group 1; group 3 (p < 0.001). Gender: group 1; group 2 (p = 0.6), group 2; group 3 (p = 0.6), group 1; group 3 (p = 0.9). BMI: group 1; group 2 (p < 0.001), group 2; group 3 (p < 0.001), group 1; group 3 (p < 0.001). Type 2 DM: group 1; group 2 (p = 0.9), group 2; group 3 (p < 0.001), group 1; group 3 (p < 0.001). HT: group 1; group 2 (p = 0.9), group 2; group 3 (p < 0.001), group 1; group 3 (p < 0.001). * Since the data were not normally distributed, the median (interquartile range 25–75%) value was given.

Table 3. Univariate and multivariate analysis of factors affecting the SARS-CoV-IgG level

	Univariate		Multivariate	
	β	*p* value	β	*p* value
Age	−123	<0.001	−70	0.03
Sex (F/M)	1,404	0.5		
BMI	−218	<0.001	−197	0.006
T2DM	−1,941	0.04		
HT	−3,780	0.001	−2,521	0.03

BMI, body mass index; T2DM, type 2 diabetes mellitus; HT, hypertension.

Results

Altogether, 360 patients (236 female, 124 male; age >18 years) who have received 2 doses of CoronaVac vaccine were enrolled in the study. Eighty-five were found to have prior COVID-19 after being evaluated with the SARS-CoV-2 IgG NCP antibody test. The seroconversion rate among 360 patients was 94%. Seroconversion was not achieved in 22 patients (19 women, 3 men). In 275 patients with non-prior infection, the antibody titers against the SARS-CoV-2 spike antigen of patients with BMI ≥30 kg/m^2 (n = 128) were significantly lower than those with BMI <30 kg/m^2 (n = 147, p = 0.001) (Table 1). In the subgroup of 85 patients with prior infection, the antibody titers in people with BMI ≥30 kg/m^2 (n = 41) were significantly lower than those having a BMI <30 kg/m^2 (n = 44, p = 0.03) (Table 1). Demographic, clinical characteristics, and antibody titers of patients with prior and non-prior SARS-CoV-2 infection are listed in Table 1.

The differences in the SARS-CoV-2 anti-spike IgG titers, age, sex, and comorbidities among different BMI groups are also listed in Table 2. The correlation analysis demonstrated that age (p < 0.001, r = −0.521) and BMI (p < 0.001, r = −0.444) were inversely correlated with SARS-CoV-2 IgG titers. In the multivariate analysis, age (p = 0.03), BMI (p = 0.006), and hypertension (HT) (p = 0.03) were found to be independent risk factors for antibody response in PwO (Table 3).

Comparison between Sexes

In the uninfected study group, the antibody levels of women was 700 (224–3,516) AU/mL; the antibody levels of men was 323 (182–789) AU/mL (p = 0.001). The antibody titers of women in the infected subgroup was 4,319 (1,743–8,480) AU/mL, and the antibody titers of men was 2,907 (1,550–7,404) AU/mL (p = 0.281) (Table 4).

Discussion

Our study demonstrated that the antibody levels against SARS-CoV-2 spike antigen after two doses of inactive SARS-CoV-2 vaccine (CoronaVac) administration are significantly lower in individuals with obesity who have or have not previously encountered with COVID-19. The European Association for the Study of Obesity (EASO) has recognized the impact of the COVID-19 epidemic on PwO. Emerging data suggest that obesity is a

Table 4. Comparison of antibody titers between sexes

	Prior infection		*p* value	Non-prior infection		*p* value
	female (*n* = 57)	male (*n* = 28)		female (*n* = 179)	male (*n* = 96)	
SARS-CoV-2, AU/mL*	4,319 (1,743–8,480)	2,907 (1,556–7,404)	0.281	700 (224–3,516)	323 (182–789)	0.001

SARS-CoV-IgG (AU/mL), severe acute respiratory syndrome-coronavirus-immunoglobulin G (arbitrary units per milliliter). Since the data were not normally distributed, the median (interquartile range 25%–75%) value was given.

risk factor for the more serious and complex course of COVID-19 in adults [10]. Therefore, PwO should be prioritized for COVID-19 vaccination [11].

In obese individuals, expression of angiotensin-converting enzyme-2 (ACE2) and transmembrane prosthetic serine 2 (TMPRSS2) is increased via phosphoinositide 3-kinase/protein kinase B/androgen receptor signaling due to hyperinsulinemia and insulin resistance. Through this pathway, the entry of SARS-CoV-2 into the cell increases [12]. Vaccines are needed to protect vulnerable individuals who obese and have associated metabolic disease. However, obesity causes a decrease in the proliferation of T and B memory cells due to the shortening of telomere length in immune cells. This leads to a decrease in the effectiveness of the vaccine and, in the long term, reduced protection [13].

Obesity leads to a chronic inflammatory process by causing dysfunctional adipose tissue [14]. Chronic stress and inflammation in adipose tissue lead to adipocyte apoptosis and the release of chemotactic cytokines, resulting in inflammatory leukocyte infiltration and increased secretion of proinflammatory cytokines [15, 16]. Chronic inflammation associated with obesity can impair macrophage activation and migration, cause generation of neutralizing antibodies and memory *T* cells, and reduce the activation of effector cells of the immune system that suppress immune functions and host defense [17, 18]. Considering these, it is thought that local and systemic chronic inflammation in obesity contributes to immune dysfunction, and as a result, the risk of COVID-19 infection increases, and the vaccine response decreases.

In patients with chronic lung, heart, and kidney disease; obesity; type 2 diabetes; and HT, especially in the elderly; COVID-19 prognosis worsened; and it presented higher mortality rates. Obesity is known to be a gateway disease for cardiovascular disorders and type 2 diabetes and other noncommunicable diseases. In addition, increased mechanical ventilation need, increased respiratory work, respiratory muscle insufficiency, and decreased respiratory compliance negatively affect the course of respiratory tract disease in PwO [19]. In our study, BMI, type 2 diabetes, HT, and age were found to have a negative effect on antibody levels.

In PwO, leptin deficiency and/or leptin resistance of immune cells adversely affect the production and activation of *T* cells and impair immune responses [20]. Adiponectin, another important adipokine closely related to obesity, has been shown to affect immunity. While leptin plays a more important role in the preparation and initiation of immune responses, adiponectin is required for inflammatory resolution with both its anti-inflammatory and insulin-sensitizing properties [21]. Thus, leptin resistance due to elevated leptin levels combined with decreased adiponectin levels in obesity contributes to poor response to infectious agents as well as increased proinflammatory cytokine production. In addition, obesity may be a factor that complicates vaccine administration due to insufficient needle length that prevents intramuscular deposition of the vaccine, thereby limiting antigen exposure to the immune system [22]. It is known that antibody responses to hepatitis B and tetanus vaccines are decreased in PwO [23]. In another study, it was reported that the serological response to influenza vaccine in PwO was similar at the beginning compared to nonobese subjects, but there was a great decrease in antibodies against influenza after 12 months [7]. In addition, studies have shown the role of high BMI in the immune response against infectious pathogens and vaccines and an increase in serious complications related to the 2009 pandemic of H1N1 influenza A [24, 25]. In the recent COVID-19 vaccine study of Pellini R et al., normal-weight participants were found to have stronger antibody titers than those who were obese [26]. In our study, BMI was found to be negatively associated with SARS-CoV-2 IgG antibody levels, and the antibody titers of PwO of both sexes were found to be lower than those of normal weight individuals, and the results were found to be consistent with the literature [27–30].

Clinical studies on effectiveness of vaccines (especially with CoronaVac) against SARS-CoV-2 in PwO are scarce, and their results are conflicting. In the study conducted by Butsch et al. [31], the effectiveness of Pfizer-BioNTech (BNT162b2 mRNA), Moderna, and Johnson & Johnson/Janssen vaccines was similar among PwO and nonobese subjects (94.8% vs. 95.4%, 95.8% vs. 94.1%, 66.8% vs. 66.9%, respectively). In our study, the seroconversion rate of patients in the non-prior SARS-CoV-2 infection arm was 83.5% in the obese group and 99.4% in the nonobese group. In a recent study with BNT162b2 mRNA vaccine, the antibody titer in individuals with abdominal obesity was found to be 2.4 times lower than those without [32]. In our study, antibody levels of nonobese subjects were found to be approximately 10 times higher than those of PwO.

Our findings showed that antibody levels were higher in women than in men in the non-prior SARS-CoV-2 infection arm. Efficient T-cell activation in women after SARS-CoV-2 infection [33, 34] was behind these findings, and this condition has been linked to the X chromosome, sex hormone, and environmental factors [35, 36].

A decrease in the number of T cells and clonal diversity, changes in the T-cell cytokine profile and a decrease in B-cell diversity and function, and a decrease in the formation of high-quality immunoglobulin are observed as people age [37]. Studies have shown that comorbidities such as HT, coronary artery disease, and congestive heart failure, which are highly prevalent in PwO, may reduce the immunogenicity of vaccines [38]. Similarly, HT and age were found to be independent risk factors for antibody response in addition to BMI in our study.

Limitations

In our study, we were not able to perform the gold standard PRNT due to technical and financial reasons. Moreover, the estimation of the protective value of the neutralizing antibodies by the method we used was based on the cutoff value of the manufacturer, not of health authorities. Therefore, our data may only provide a perspective on the protection capability of the vaccine in PwO compared to nonobese controls.

Conclusion

SARS-CoV-2 IgG antibody levels against CoronaVac vaccine were found to be significantly lower in PwO compared to nonobese subjects in both groups with prior and non-prior infection. BMI was determined as an independent risk factor for antibody titer. In PwO, it may be crucial to follow up antibody titers, and additional boosters should be delivered accordingly for optimal protection.

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Statement of Ethics

The study was approved by the local Institutional Review Board, the Ethics Committee of the Cerrahpasa Faculty of Medicine, reference date and number: 05.05.2021-90353, and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors provided substantial contribution to the design and implementation of this study and to the generation of the manuscript. The contributions of each author are as follows: V.D. Yumuk and B. Kocazeybek conceived design and purpose of the work. Z. Kara, R. Akçin, and H.Ö. Dinç analyzed the data. V.D. Yumuk, Z. Kara, and A.N. Demir interpreted the results based on the available literature and drafted the manuscript. V.D. Yumuk made critical revisions. V.D. Yumuk and B. Kocazeybek provided the final version of the article.

Data Availability Statement

The data used and analyzed during the current scoping review are available from the corresponding author on reasonable request.

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