ORIGINAL RESEARCH

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The Older Population's Antibody Response to SARS-CoV-2 Inactivated Vaccine (CoronaVac) is Independent to Vitamin D Levels

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Abstract

Objective: The purpose of this study was to determine how the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) inactivated vaccine antibody response and vitamin D levels in the older population are related.

Materials and Methods: This study included people over the age of 60 who received their second dose of the SARS-CoV-2 inactivated vaccine after 28 days. Immunoglobulin G antibodies against SARS-CoV-2 spikes were measured; levels equal to or greater than 1 U/mL were classified as seropositive, and levels below 1 U/mL were classified as seronegative. Serum 25-hydroxyvitamin D levels were evaluated in the participants; levels below 30 nmol/L were classified as low, and levels above 30 nmol/L were classified as normal.

Results: A total of 188 patients were included. A total of 152 people (80.9%) were found to be positive for the antibodies. The median [interquartile range (IQR)] age of the seropositive individuals was 71 (60-94) and the median (IQR) age of seronegative individuals was 72 (64-86) (p=0.272). While the vitamin D level was below 30 in 115 (75.6%) of the seropositive group, the vitamin D level was below 30 in 26 (70.9%) patients in the seronegative group (p=0.822).

Conclusion: In this study, we examined the association between vitamin D levels and seroconversion rate after the second dose of SARS-CoV-2 inactivated vaccine. There were no differences between the seropositive and seronegative groups in terms of vitamin D levels. In another context, it was discovered that vitamin D level has no effect on antibody response.

Keywords: COVID-19, immunology, older people, spike antibodies, vitamin D

Introduction

Even while the coronavirus disease-2019 (COVID-19) pandemic's most dangerous effects have all but disappeared, the consequences of the new variations persist, particularly in populations of older people and immunocompromised patients. Not only did the virus lose its virulence, but vaccination also put a stop to the pandemic.

Serum vitamin D insufficiency has been linked to an increased incidence of COVID-19, as well as increased severity and mortality of the disease, according to numerous observational studies (1-4). A substantial correlation was discovered in a large observational population study between the probability of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and suffering severe illness if infected

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and serum vitamin D insufficiency evaluated before to the pandemic (5). On the other hand, factors other than serum vitamin D levels that affect the likelihood of COVID-19 infection include age, sex, comorbidity, and geographic location (6-8).

Vitamin D is essential for the regulation of human immune function, although it is best known for its effects on calcium homeostasis (9). The active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25(OH)2D] is a pro-inflammatory in relation to monocytes and macrophages. It targets mitogen activated protein kinase phosphatase 1 (10) to regulate mammalian target of rapamycin. It has been shown to be an inhibitor of cytokine production (11) and phospholipase C in naive T cells. By inducing gamma 1 (12), it is used to support T cell activation and classical T cell receptor signaling.

25-hydroxyvitamin D [25(OH)D3], is the primary form of vitamin D that is circulating. Optimal vitamin D levels are indicated by low blood levels of the vitamin. This disease is more common in older people and is associated with increased systemic inflammation (13,14). Supplementation with vitamin D has been associated with elevated levels of circulating [25(OH)D3] in older individuals connected to the cutaneous varicella zoster virus antigen (15). A reduction in early inflammatory monocyte infiltration and T to the antigen challenge site have both been shown to considerably improve the response to challenge at concentrations of less than 75 nmol/L. Higher uptake was correlated with increased uptake of cells.

Studies are typically planned with consideration for all age groups, but there are very few that concentrate specifically on the older population with its many comorbidities, and there are still many unanswered concerns regarding immunization responses (16).

This study aimed to assess the relationship between antibody response and serum vitamin D levels in a geriatric population vaccinated with CoronaVac.

Materials and Methods

In this study, the files of patients who applied to the Hacettepe University Faculty of Medicine Hospital geriatrics polyclinic between August 2021 and September 2021 were retrospectively scanned between November 2022 and December 2022. This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision number: 2022/22-30, date: 27.12.2022). The trial comprised 188 older outpatients over 60 who had received their second dose of the SARS-CoV-2 inactivated vaccine (CoronaVac) after 28 days.

Criteria for inclusion in the study: (1) being over 65 years of age, (2) those who agree to participate in the study, (3) having the ability to understand and answer the questions asked.

Exclusion criteria: (1) uncooperative and unoriented patients, (2) patients for whom comprehensive geriatric evaluation cannot be performed, (3) patients who do not agree to provide serum samples for the study of antibody response and Vitamin D level parameters, (4) patients with COVID-19 confirmed by SARS-CoV-2 real-time polymerase chain reaction or thoracic computed tomography or who had clinical suspicions of COVID-19, (5) under immunosuppressive treatment, dementia, and dialysis.

The participants' demographic information, chronic disease, number of medication, polypharmacy (>5), Charlson comorbidity index (CCI), and malnutrition [mini nutritional assesment-short form (MNA-SF)] status were noted. MNA-SF to perform nutritional scanning, >11 scores were considered normal, 8-11 points indicated malnutrition risk, and 7 points indicated malnutrition (17,18). The comorbidity status of the individuals was assessed using the commonly used CCI (19).

SARS-CoV-2 Immunoglobulin G (IgG) Antibody Assay

Blood samples were obtained from patients to measure their IgG levels for SARS-CoV-2. Serum samples were centrifuged at 4000 rpm for 10 min. The samples were stored at -20˚C. IgG was detected using the Atellica IM SARS-CoV-2 IgG (sCOVG) test (11207386, California, USA). All samples and the SARS-CoV-2 spike protein receptor binding site were processed on the Atellica IM 1600 analyser. The immunological test called Atellica IM sCOVG uses chemiluminescent technology and has a measurement range of 0.50-150.00 index (U/mL). The sensitivity of the Atellica IM sCOVG assay was evaluated using the 1st World Health Organization international standard for anti-SARS-CoV-2 immunoglobulin (human), national institute for biological standards and control code 20/136. The concentration of the reference standard corresponding to the cut-off value of the 1.00 index (U/mL) was used (20). SARS-CoV-2 spike-specific IgG antibodies were identified; values >1 U/mL were considered seropositive and <1 U/mL seronegative.

Vitamin D Measurement by High-performance Liquid Chromatography (HPLC) Method

Vitamin D on Agilent 1100 HPLC device. Acetonitrile as a mobile phase for measurement a solution containing the mixture was used. Stable a vitamin D derivative internal standard was used as. Flow rate of the column 40-50 bar. The pressure was 0.7 mL per minute. Column temperature was 25˚C. 25- at a flow rate of 0.7 mL per minute retention time of 25(OH)D3 peak is 4.2 minutes, retention of internal standard His time was 7.1 minutes. Measurement 265 nm wave was performed with the help of a ultraviolet detector on the neck eld after extraction (21). Serum 25(OH)D3 levels were measured; values below 30 nmol/L were categorized as low, and values above 30 nmol/L were categorized as normal.

Statistics

The statistical analyses were performed using IBM SPSS version 23.0. To ascertain whether or not the variables were regularly distributed, both visual (histograms and probability plots) and analytical techniques were used. For normally distributed variables, descriptive statistics were displayed as mean ± standard deviation; for non-normally distributed data, as median [interquartile range (IQR)] and for nominal variables, as number of cases and (%). When there were two groups, the Mann-Whitney U test was used to compare group differences in median values. For categorical variables, data were compared using the chi-square test or Fisher's exact test and the Bonferroni correction was applied when necessary. Statistical significance was defined as $p<0.05$.

Results

The study included 188 patients, whose median (IQR) age ranged from 67 to 75. There were 101 (59%) female patients. The seropositivity ratio was 80.9% (n=152). Seropositive group, SARS-CoV-2 spike IgG serum level U/mL, median (IQR) was 4.6 (2.5-10), and seronegative group was 0.56 (0-0.6) ($p<0.0001$). Regarding age, sex (female), nutrition, polypharmacy, and concomitant illnesses apart from asthma ($p=0.272$, $p=0.779$, $p=0.196$, $p=0.822$ respectively), there were no statistically significant between the seropositive and seronegative groups. The CCI scores were higher in the seronegative group ($p=0.023$) (Table 1).

While the seropositive patients in the low vitamin D group were 115 (75.6%), the seronegative group patients were 26 (70.9%) ($p=0.822$) and the seropositive patients in the normal vitamin D group were 37 (24.4%), the seronegative group patients were 10 (29%) ($p=0.596$).

The seropositivity distribution according to vitamin D levels (µg/L) is shown in Figure 1. The median vitamin D level was found to 19 µg/L (0.5-94) in the seropositive group and median of vitamin D level in seronegative group was 19 µg/L (5-52), in both the seropositive group and the seronegative group, and no difference was observed.

Discussion

It is a well-known fact that morbidity and mortality from SARS-CoV-2 infection occur more frequently in older patients than in younger adults, taking into account a number of factors such as physiological changes and comorbidities brought about by aging. Low vitamin D levels are one of these age-related consequences. The rates of acute respiratory infections such as SARS-CoV-2 and influenza are linked to vitamin D deficiency (22). For those at higher risk of viral infections, studies recommend using higher doses of vitamin D. However, significant toxicity

Table 1. Clinical and demographic characteristics, comparison between antibody positive and negative groups after 28 days after the 2nd dose of vaccination group

	Seropositive group 152 (80.9%)	Seronegative group 36 (19.1%)	p
Age, years	71 (60-94)	72 (64-86)	0.272
Gender (female)	89 (58.6%)	22 (61.1%)	0.779
Low vitamin D group [25(OH)D3] <30 (µg/L)]	115 (75.6%)	26 (70.9%)	0.822
Normal vitamin D group [25(OH)D3] >30 (µg/L)]	37 (24.4%)	10 (29%)	0.596
Comorbidities			
HT	107 (70.4%)	28 (77.8%)	0.376
DM	65 (42.8%)	19 (52.7%)	0.277
Dementia	9 (5.9%)	1 (2.7%)	0.450
CVD	40 (26.3%)	9 (25%)	0.872
Depression	16 (10.5%)	2 (5.5%)	0.362
CRF	6 (3.9%)	2 (5.5%)	0.667
COPD	12 (7.9%)	3 (8.3%)	0.930
Asthma	12 (7.9%)	9 (25%)	**0.003***
Malnutrition (MNA <7)	13 (9%)	2 (5.5%)	0.196
Polypharmacy	88 (59.1%)	22 (61.1%)	0.822
CCI score, median	1 (0-2)	2 (1-3)	**0.023***
SARS-CoV-2 spike IgG serum level U/mL, median (IQR)	4.6 (2.5-10)	0.56 (0-0.6)	**<0.0001***

Variables were presented as n (%), mean ± standard deviation or median (IQR)
*Significance at $p<0.05$
[25(OH)D3]: 25-hydroxyvitamin D, CVD: Cardiovascular diseases, HT: Hypertension, DM: Diabetes mellitus, CRF: Chronic renal failure, COPD: Chronic obstructive pulmonary disease, MNA: Mini nutritional assessment, CCI: Charlson comorbidity index, IgG: Immunoglobulin G, IQR: Interquartile range, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

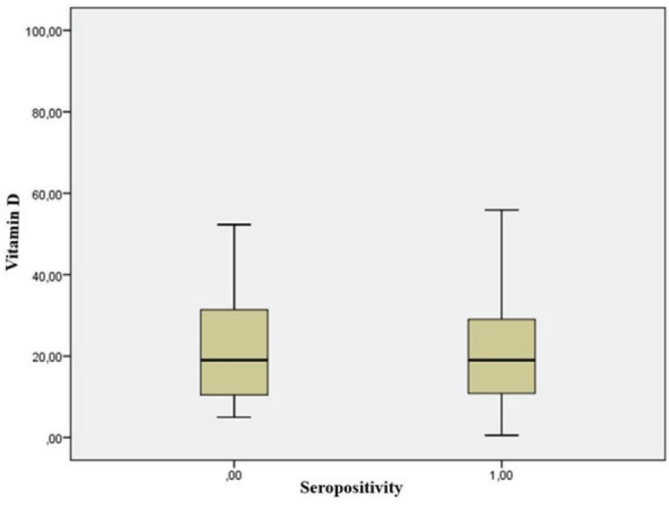

Figure 1. Seropositivity distribution according to vitamin D levels (µg/L)

and hypervitaminosis have recently been observed, and caution is required in this regard (23). On the other hand, it has been suggested that regular oral vitamin D intake of 2000 IU per day (without supplementation) is safe and protective against acute respiratory distress syndrome, especially for patients with vitamin D deficiency (24). Numerous observational studies have looked into the relationships between the immunogenicity of the SARS-CoV-2 vaccine and vitamin D levels, but these have yielded conflicting results: some have found higher post-vaccination anti-spike antibody titers in individuals who used vitamin D supplements or had higher circulating levels of vitamin D (25,26); they have reported findings opposite to those of other studies (27-29).

Vitamin D has been demonstrated to have immunomodulatory and antiproliferative effects on T cells, which reduce the expression of pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha (30). Similar research indicates a connection between vitamin D levels in viral infections and vaccination responses. The ability to affect the adaptive immune response likely causes the regulatory impact. It has been suggested that vitamin D may enhance CD4+ lymphocyte production while reducing the proliferation of helper T cells. By turning B cells into plasma cells, this can boost the generation of virus-specific antibodies (31).

It is well known that active vitamin D (1-alpha, 25-dihydroxy vitamin D3) controls the immune system's adaptive response, which is produced naturally (32,33). Typically, vitamin D acts as a hormone to enhance the immunological response (34,35). Therefore, vitamin D may not make the expected contribution to the immune response because our study was conducted on an aged population, and the adaptive immune response was decreased in this group. However, several studies in the literature that included various age groups produced findings that were comparable to our findings (28).

In our study, similar to some studies in the literature, we could not detect a connection between vitamin D levels and sCOVG response. We believe that these results may have been affected by the fact that the patients received an inactive vaccine and that 28 days or more had passed, which is a long time for an inactive vaccine. Additionally, in another study that used the vaccine, no connection was found between vitamin D deficiency and immune response to the mRNA vaccine (36).

Another randomized, placebo-controlled study examined the effects of vitamin D supplementation and inactivated influenza vaccine in older participants and found that vaccine antibody titers did not change after vitamin D supplementation (37).

Two doses of inactive vaccine were used in our study; this may be considered insufficient, considering that inactivated vaccination produces limited immunity and show cumulative effects. However, a different randomized controlled trial examining the link between vitamin D levels and immune response following the second dosing showed the same results despite the use of an mRNA vaccine (27). According to one study, the highest antibody response was achieved three weeks after receiving the mRNA vaccine and continued until the eighth week. The relationship between age and antibody response was inverse, with vitamin D deficiency negatively affecting the antibody response. Additionally, only 97 participants were included in this study. However, serial antibody assessments performed after the first 4 weeks of vaccination increased the reliability of the study (38).

Studies assessing the connection between various inactivated vaccine immunogenicity and vitamin D produced similar findings. A meta-analysis that examined the relationship between vitamin D insufficiency and immunogenicity of influenza vaccination revealed that vitamin D levels did not influence the immunological response. Additionally, there was no discernible connection in a trial that assessed the immunogenicity of a different inactivated vaccination, specifically hepatitis B, in individuals who were vitamin D deficient (39).

Study Limitations

One of the limitations of our study is that the findings would have been stronger if serial antibody and vitamin D tests had been performed before and after vaccination. It is important to remember that various factors, such as comorbidities and nutrition, can affect an individual's immune response to the vaccine. Another important issue is that we tested [25(OH)D3] not the active form of vitamin D, as in many studies in the literature. In this study, we administered MNA-SF to patients due to our limited understanding of the population's dietary preferences and micronutrient utilization. At the beginning of our research and literature review, it was anticipated that vitamin D complement

activation would have particularly adaptive and hormonal effects for the older population. However, neutralizing or non-neutralizing antibodies specific to inactivated vaccines cannot be produced by vitamin D alone. Understanding metabolic and molecular mechanisms through a prospective, comprehensive population study of vitamin D levels and replacement will help determine the effects of vitamin D on cell-mediated immunity during aging.

Conclusion

To look at the antibody levels for additional vaccines in older individuals, randomized controlled trials with larger populations are required.

Ethics

Ethics Committee Approval: Between November and December of 2022, the Hacettepe University Hospital retrospectively scanned the biochemical values and demographic data of the study participants with decision number 2021/17-05 (KA-21084). This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision number: 2022/22-30, date: 27.12.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Z.Ş., A.O.B., D.K., M.G.H., Concept: Z.Ş., A.O.B., D.K., C.A., F.A., M.G.H., Design: Z.Ş., M.G., S.D., M.H., C.A., B.B.D., M.C., M.G.H., Data Collection or Processing: Z.Ş., M.G., S.C., Analysis or Interpretation: Z.Ş., A.O.B., M.G., S.C., B.Ç., S.Ü., Literature Search: Z.Ş., M.H., M.G.H., Writing: Z.Ş., A.O.B., M.G.H.

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