

CLINICAL STUDY

Investigation of SARS-CoV-2 antibody levels after COVID-19 vaccine in chronic hepatitis B patients

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ABSTRACT

AIM: The aim was to compare SARS-CoV-2 IgG antibody levels in chronic hepatitis B patients and healthcare personnel selected as the control group and to determine factors such as age, gender, vaccine type, and number of vaccines that may affect the antibody levels.

MATERIALS AND METHODS: 87 chronic hepatitis B (CHB) patients followed in Ankara Training and Research Hospital Infectious Diseases Clinic and Mamak State Hospital Infectious Diseases outpatient clinic and 89 healthcare personnel selected as the control group were included in the study.

SARS-CoV-2 IgG antibody levels in the serum samples of patients and healthcare personnel who received the COVID-19 vaccine were studied with the ELISA method in the Microbiology Laboratory of Ankara Training and Research Hospital, using a commercial ELISA kit (Abbott, USA) in line with the recommendations of the manufacturer. In the study, SARS-CoV-2 IgG levels were compared in CHB patients and healthcare personnel. In addition, the relationship between SARS-CoV-2 antibody level, gender, average age, natural history of the disease, number of vaccinations, vaccine type (Coronavac TM vaccine alone, BNT162b2 vaccine alone or Coronavac TM and BNT162b2 vaccine (heterologous vaccination)), treatment duration of CHB was investigated. Statistical analyses were made in the SPSS program. A value of $p \leq 0.05$ was considered statistically significant.

FINDINGS: A total of 167 people, including 87 CKD patients and 80 healthcare personnel as the control group, were included in the study. SARS-CoV-2 IgG antibody levels were detected above the cut-off level in the entire study group, regardless of the vaccine type. No difference was detected in SARS-CoV-2 IgG titers after COVID-19 vaccination between CHB patients and healthcare personnel. There was a statistically significant difference in SARS-CoV-2 IgG antibody levels among individuals participating in the study according to vaccine types. Compared to those who received Coronavac TM vaccine alone, the average SARS-CoV-2 IgG level was found to be statistically significantly higher in those who received BNT162b2 vaccine alone or heterologous vaccination with Coronavac TM + BNT162b2 vaccine. There was no difference between the groups in terms of age, gender, number of vaccinations, natural transmission of the disease, and duration of antiviral therapy in the CHD patient group.

CONCLUSION: As a result, SARS-CoV-2 IgG antibody levels above the cut-off value were achieved with Coronavac TM and BNT162b2 vaccines in both CHD patients and healthy control groups. However, both CHD patients and healthcare personnel had higher antibody levels than those who received BNT162b2 alone or those who received heterologous vaccination had higher antibody levels than those with Coronavac TM alone. Therefore, if there are no contraindications, BNT162b2 vaccine may be preferred in CHB and health personnel (Tab. 2, Ref. 14). Text in PDF www.elis.sk

KEY WORDS: chronic hepatitis B, healthcare personnel, COVID-19, vaccination, SARS-CoV-2 IgG.

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Introduction

The pandemic caused by the SARS-CoV-2 virus, the causative agent of COVID-19 disease, is an important public health problem all over the world and in Turkey (1, 2). During the COVID-19 pandemic, COVID-19 vaccines were developed in a short period of one year and began to be used all over the world with emergency use approval (3). Emergency use approval has been obtained for 21 of the COVID-19 vaccines, and different COVID-19 vaccines have been put into use in many countries. In Turkey, among the

COVID-19 vaccines, Coronavac TM (Sinovac, China) inactivated virus vaccine and BNT162b2 (Pfizer-Biontech, USA, Germany) mRNA vaccine have been approved for clinical use and are widely used in mass vaccination.

The aim of this study was to compare SARS-CoV-2 IgG antibody levels in chronic hepatitis B patients and health personnel selected as the control group and to determine whether there is a relationship between antibody levels (titers) and gender, age, vaccine type, number of vaccines, whether they have the disease actively or not, and duration of treatment for CHD patients.

Materials and methods

The study was carried out in cooperation with MoH Ankara Training and Research Hospital Infectious Diseases Clinic and Mamak State Hospital Infectious Diseases Polyclinics. The study included 87 (52.1%) CHB patients who applied to Ankara Training and Research Hospital Infectious Diseases outpatient clinic and Mamak State Hospital Infectious Diseases outpatient clinic between 11.08.2022 and 11.04.2023, and 80 (47.9%) working in these hospitals, selected as the control group (healthcare personnel) were included. Demographic data such as age and gender of chronic hepatitis B patients (CHB) and healthy control group, which vaccines (inactive and/or mRNA) they have received for COVID-19, the number of vaccines they have received, date of last dose of vaccination, COVID-19. Whether they had an infection or not was recorded on the follow-up forms. Moreover, information about the antiviral treatment and treatment duration received by CHB patients was also recorded in the patient follow-up forms. Inclusion criteria for CHB patients:

1. Being 18 years or older
2. Agreeing to sign the informed consent form
3. Receiving outpatient follow-up and treatment with a diagnosis of chronic hepatitis B and receiving the COVID-19 vaccine.
4. At least a month or more have passed since the COVID-19 vaccine.

Inclusion criteria for the healthcare personnel in the control group are:

1. Being over 18 years of age or being 65 years of age or younger
2. Underlying immunosuppressive disease, chronic hepatitis B, or chronic hepatitis C absence
3. Getting vaccinated against COVID-19
4. It was defined as at least one month or more having passed after the COVID-19 vaccine.

The patients and healthcare personnel consisted of adults who were administered Coronavac TM (Sinovac, China) inactive vaccine alone or BNT162b2 (Pfizer-Biontech, USA, Germany) mRNA vaccine alone or heterologously administered Coronavac TM and BNT162b2 vaccine. Individuals who have received at least one dose of vaccine measured SARS-CoV-2 IgG antibody levels at least one month or later after the last vaccine, using a commercial SARS-CoV-2 IgG II Quant ELISA kit (Abbott, USA) and ELISA in the Microbiology Laboratory in accordance with the manufacturer's recommendations were investigated.

The cut-off value for SARS-CoV-2 IgG antibody titer was accepted as 50 AU/ml, and antibody levels above this value were considered positive. (4).

SARS-CoV-2 IgG antibody levels were compared in CHB and healthcare personnel. Additionally, the relationship between SARS-CoV-2 IgG level, gender, average age, number of vaccinations, vaccine type [(inactive virus vaccine (Coronavac TM) and mRNA vaccine (BNT162b2)], and actively having the disease was statistically analyzed.

Statistical analyses were performed with the SPSS program. Kruskal–Wallis and Mann–Whitney U tests were used in statistical evaluations. A value of $p \leq 0.05$ was considered statistically significant.

For the study, ethics committee approval numbered E-22/1022 was obtained from the Ethics Committee of Health Sciences University, Ankara Training and Research Hospital on 11.08.2022 and written consent was obtained from the participants of the study.

Findings

Of the 167 people who participated in the study, 108 (64.7%) were women and 59 (35.3%) were men. The age range of the participants was between 22–77, the average was 45.46 ± 11.34 years.

Of the total 87 CHB patients, 44 (50.6%) were female and 43 (49.4%) were male. The age range of the patients was between 22–77 years, the average was 48.52 ± 12.18 years. 68 (78.2%) of the patients were receiving antiviral treatment. 32 (36.8%) of the CHB patients had a history of COVID-19 infection. 72 of the patients had received the BNT162b2 vaccine and 32 had the Coronavac TM vaccine. 31 of the patients (35.6%) had concomitant diseases, these diseases were diabetes in 10 patients and hypertension in 13 patients.

In the CHB patient group ($n=87$), no statistically significant difference was detected between gender and SARS-CoV-2 IgG level ($p=0.8349$).

Of the total of 80 healthcare personnel, 64 (80%) were women and 16 (20%) were men. The average age of healthcare personnel was 42.14. Among the healthcare personnel, 12 patients had diabetes and 20 patients had hypertension. There was no statistically significant difference between healthcare personnel and CHB patients in terms of comorbidities.

The rate of COVID-19 in healthcare personnel was statistically higher than in CHB patients ($p=0.001$, 63.8% in healthcare personnel, 36.8% in CHB patients, respectively). In terms of the number of vaccinations, the average number of vaccinations in healthcare personnel was 3.61, while it was 2.82 in CHB patients. The number of vaccinations in healthcare personnel was statistically higher than in CHB patients ($p=0.000$). The rate of Coronavac TM vaccination in healthcare personnel was higher than in CHB patients ($p=0.000$). The rate of BNT162b2 vaccination in CHB patients was higher than in healthcare personnel ($p=0.036$).

When healthcare personnel and CHB patients were compared in terms of SARS-CoV-2 IgG level, no statistically significant difference was detected (while the average SARS-CoV-2 level in

healthcare personnel was 11870 AU/ml, this rate was determined to be 10.230 AU/ml in healthcare personnel ($p=0.293$).

No statistically significant difference was detected between gender and SARS-CoV-2 IgG antibody level in CHB patients ($n=87$) ($p=0.834$; the mean SARS-CoV-2 IgG in women was 12112.77, while it was 11623.26 in men).

There was no difference in SARS-CoV-2 IgG antibody levels in CHB patients under the age of 50 and over the age of 50 ($p=0.288$, while the average antibody level under the age of 50 was 10590.57, the average antibody level in those over the age of 50 was 13065.73).

Although there was no statistically significant difference between the number of vaccines administered in CHB patients and SARS-CoV-2 IgG levels, the antibody level was higher in those who received two or more vaccines ($p=0.131$; the antibody level was 5434.67 in those who received one vaccine and 12347.58 in those who received two or more vaccines).

No statistically significant difference was detected between gender and SARS-CoV-2 IgG level in healthcare personnel ($n=80$) ($p=0.901$, while the antibody level in women was 10166.64; in men it was 10487.75).

No statistically significant difference was detected in terms of SARS-CoV-2 IgG levels in healthcare personnel under the age of 50 and over the age of 50 ($p=0.305$).

Although there was no statistically significant difference between the number of vaccines administered and the SARS-CoV-2 IgG level in healthcare personnel, the antibody level was found to be higher in those who received two or more vaccines ($p=0.416$; the antibody level was 5003.5 in those who received a single vaccine ($n=2$). While the antibody level in those who received two or more vaccines ($n=78$) was 10364.9).

Although SARS-CoV-2 IgG levels were detected to be higher in those who received two or more vaccines in both groups than

in those who received one vaccine, no statistically significant difference was detected ($p=0.097$). SARS-CoV-2 levels by number of COVID-19 vaccinations are shown in Table 1.

Receiving a single vaccination or two or more vaccinations did not cause a statistically significant difference in the SARS-CoV-2 IgG antibody level between those who had COVID-19 and those who did not ($p=0.496$).

There was no statistically significant difference between having COVID-19 and SARS-CoV-2 IgG level among all participants (respectively; while the average antibody level in those who had COVID-19 was 10595, the average antibody level in those who did not have COVID-19 was 11569. $p=0.532$).

It was determined that 84 (50.3%) of the participants had previously had COVID-19. It was determined that 103 of the participants had the Coronavac TM vaccine and 128 had the BNT162b2 vaccine. 62 (37.1%) of the participants had at least one accompanying disease. Of accompanying diseases; 12 patients had diabetes and 20 patients had hypertension. The average SARS-CoV-2 IgG antibody level of the study participants was 11085 ± 10042.210 (minimum 155, maximum 40 000). The number of COVID-19 vaccines received by the study participants varied between 1-6, the average was 3.21 ± 1.135 .

Only one statistically significant difference was detected in SARS-CoV-2 IgG antibody levels among the individuals participating in the study according to vaccine types (Kruskal–Wallis test; $p=0.001$). This difference was: Those who received Coronavac TM and BNT162b2 vaccine (Mann–Whitney U test; $U=729$; $Z=-3529$; $p=0.0001$) and those who received Coronavac TM and Coronavac TM + BNT162b2 (Mann–Whitney U test; $U=742$; $Z=-3.44$; $p=0.001$) was caused by differences in SARS-CoV-2 IgG antibody levels. Compared to those who received Coronavac TM vaccine alone, the average SARS-CoV-2 IgG level was found to be statistically significantly higher in those who received BNT162b2 vaccine alone or heterologous vaccine with Coronavac TM + BNT162b2 vaccine. Coronavac TM vaccine alone, average SARS-CoV-2 IgG levels in those who received the BNT162b2 vaccine alone and those who received the heterologous vaccine with Coronavac TM + BNT162b2 vaccine, respectively; were 5885.31, 13460.3 and 11.878.83 AU/ml (Tab. 2).

Discussion

The causative agent of COVID-19 disease is the SARS-CoV-2 virus, which was first seen in the city of Wuhan in China in December 2019 and spread all over the world from there, causing a pandemic. COVID-19 can affect many organs and systems other than the respiratory system, including the cardiovascular system, gastrointestinal system, and neurological systems. Angiotensin-converting enzyme-2 (ACE-2) receptors, to which the SARS-CoV-2 virus attaches on the host cell, are also present in the gastrointestinal tract and liver, in addition to lung epithelial cells. For this reason, in addition to diarrhea and loss of appetite in COVID-19 patients, abnormalities in liver function tests can be detected in more than 50% of patients (5, 6). Liver inflamma-

Tab. 1. SARS-CoV-2 IgG levels by number of COVID-19 vaccinations.

Number of vaccinations	SARS-CoV-2 IgG level average (AU/ml)	p
single vaccine	5326	0.097
Those who have received two vaccinations	9172	
Those who have received three vaccinations	12556	
Those who have received four vaccinations	9449	
Those who have received five vaccinations	15688	
Those who have received six vaccinations	21071	

Tab. 2. SARS-CoV-2 IgG levels in those who received the Coronavac TM vaccine alone, BNT162b2 vaccine alone, and those who received the Coronavac TM + BNT162b2 vaccine and heterologous vaccine

Vaccine	Number (n)	SARS-CoV-2 IgG titer (AU/ml)	P
CoronavacTM	39	5885.31	0.001**
BNT162b2	64	13,460.3	
CoronavacTM+BNT162b2	64	11,878.83	

** $p<0.01$ significant

tion in COVID-19 patients is due to the direct effect of the virus on the liver, hepatotoxic drugs, or coinfection of COVID-19 and hepatitis B infection. Additionally, tocilizumab and corticosteroids used in the treatment of patients with COVID-19 infection may also cause HBV reactivation. Therefore, vaccination of chronic hepatitis B patients against COVID-19 infection is an appropriate preventive approach (5).

The World Health Organization (WHO) states that approximately 257 million people worldwide are affected by chronic hepatitis B infection, and HBV infection causes approximately 900,000 deaths every year. Additionally, it often results in complications of cirrhosis and hepatocellular carcinoma. It is still unclear whether COVID-19 worsens clinical findings in CHB patients. (5). There are a limited number of studies investigating antibody levels after COVID-19 vaccination in CHB patients (7–9).

In the study we presented, no statistically significant difference was detected in terms of SARS-CoV-2 IgG antibody titers after COVID-19 vaccinations in healthcare personnel and CHB patients. No statistically significant difference was detected between SARS-CoV-2 IgG antibody titers and gender, average age, number of vaccinations, and status of actively having the disease. In our study, we found that the SARS-CoV-2 IgG antibody level was only affected by the vaccine type (inactive vaccine or mRNA vaccine) which was found to show a significant difference. SARS-CoV-2 IgG antibody titer was statistically significantly higher in those who received BNT162b2 mRNA vaccine alone or heterologous vaccine in the form of BNT162b2 inactivated Coronavac TM vaccine than in those who received Coronavac TM inactivated vaccine alone.

Although the effectiveness of the COVID-19 vaccine has been evaluated in patients with non-alcoholic fatty liver disease and liver transplantation, there are not enough studies evaluating the effectiveness of the inactivated vaccine in CHB patients.

It is not yet clear whether the various COVID-19 vaccines are safe and produce adequate immune responses in CHB patients at different stages. Xiang et al (7) in their study of 284 CHB patients, 81 unvaccinated patients, 54 patients who had received the first dose of vaccine, and 149 patients who had received the second dose of vaccine were included in the study. In the plasma samples of the patients, receptor binding domain (RBD), anti-SARS-CoV-2 spike protein (anti S-RBD IgG) and neutralizing antibodies (N Ab) were investigated. In the study, anti-S-RBD IgG and N Ab seropositivity rates were reported as 87.25% and 74.5%, respectively, in CHB patients who received two doses of vaccine. Additionally, anti-S-RBD-IgG seropositivity in CHB patients who received two doses of vaccine was reported by Tanriover et al in Turkey. (10) was found to be similar (89.7%) to the CoronaVac TM vaccine study. In the same study, antiS-RBD IgG level (76%) was reported to be higher in CHB patients than in those with chronic liver disease. In the study, it was reported that both antiS-RBD IgG and N Ab levels increased significantly after completing the two-dose vaccine regimen (7).

In our study, although the SARS-CoV-2 IgG level increased after two or more vaccinations in those who received a single dose of vaccine, no statistically significant difference was

detected between the number of vaccinations and the antibody level. In our study, the mean SARS-CoV-2 IgG level was statistically significantly higher in both CHB patients and health personnel who received BNT162b2 vaccine alone or who received heterologous vaccine with Coronavac TM + BNT162b2 vaccine compared to those who received Coronavac TM vaccine alone. These results suggest that having at least two doses of vaccine for inactivated vaccines or having mRNA vaccine after an inactivated vaccine may provide a higher level of antibody response.

It has been reported that the antibody response to COVID-19 vaccines is at desired levels despite the suppression of the immune system in CHB patients.

When Xiang et al (7) compared seropositivity response and antibody titers with sex, age, antiviral therapy, and body mass index in patients with CHB, anti-Anti-S-RBD IgG antibody titers they found higher in patients younger than 40 years of age. In the same study, the rate of neutralizing antibody seropositivity in women was reported to be increased. In the study we present, we did not detect a significant difference between SARS-CoV-2 IgG levels between being over 50 years old and under 50 years old in both CHB patients and healthcare personnel. Similarly, no difference was found between gender, whether the disease was active or not, and antibody titers. Additionally, no significant difference was found between treatment duration and antiviral treatment option (tenofovir or entecavir) in CHB patients. In the literature, it has been reported that young individuals and women who received inactivated vaccines had a strong humoral immune response to the vaccine (7, 10). Additionally, it has been reported that the NAb titer was significantly higher in those who took nucleotide analogue antiviral drugs than in those who did not (7). Possible reasons for this are: Long-term antiviral treatment may suppress viral replication, restore the impaired immune system by improving the functions of circulating dendritic cells, natural killer cells and T cells, and stimulate the production of IFN- λ 3 by nucleotide analogs (7, 11). In our study, there was no difference in SARS-CoV-2 IgG antibody titer between those receiving tenofovir treatment and those receiving entecavir treatment in CHB patients. In our study, there was no statistically significant difference when the antibody levels of CHB and health personnel were compared.

He et al (9) in their study of 362 KHBs and 87 healthy subjects, they analyzed anti-spike IgG, anti-receptor binding domain (RBD), IgG antibody levels, SARS-CoV-2-specific B cells and adverse events (adverse events) at months 1, 2, and 3 at intervals of at least 21 days before full dose vaccination with inactivated vaccine. They analyzed specific B cells and vaccine-related adverse events. Adverse events were found to be mild and self-limiting in both the CHD and control groups, with similar frequency in both groups. While anti-spike IgG, anti-receptor binding domain (RBD) IgG antibody seropositivity rates were similar, antibody titers were found to be low at 1 month in CHB patients.

Compared to the healthy control group, anti-spike IgG, anti-receptor binding domain (RBD) IgG antibody levels were detected higher in HBsAg-positive CHB patients at 3 months, and a slower

decline in antibody titers was observed. While the frequency of RBD-specific B cells was found to be positively correlated with anti-RBD IgG titers, liver cirrhosis, antiviral treatment, HBV DNA, ALT, AST levels and total bilirubin were reported not to correlate with anti-RBD IgG titers. As a result, it has been reported that inactivated COVID-19 vaccines are well tolerated in CHB patients and produce an effective antibody response against SARS-CoV-2. In our study, we determined that SARS-CoV-2 IgG antibody titer caused an antibody response much higher than the cut-off value of 50 AU/ml in CHB patients receiving Coronavac TM vaccine. In the study we present, Unlike the He et al (9) study, we found that patients who received mRNA vaccine alone (BNT162b2 vaccine) or BNT162b2 vaccine following Coronavac TM vaccine (heterologous vaccination) developed a statistically higher rate of SARS-CoV-2 IgG antibody response.

In the study by Dib et al (12) of 140 patients who underwent solid organ transplantation, 62 had a homologous (three doses of BNT162b2) and 78 had a heterologous vaccine schedule (two doses of CoronaVac followed by a BNT162b2 booster). Booster dose, on average 21.3 weeks after primary vaccination has been implemented. Total antibody seropositivity was determined as 82.3% in those who received homologous vaccine, 65.4% in those who received heterologous vaccine, and neutralizing antibody positivity was 77.4% and 55.1%, and both antibody responses were reported to be higher in homologous vaccine patients compared to the heterologous vaccine group. In the same study, the number of SARS-CoV-2-specific T cells secreting IFN- γ and IL-2 did not differ significantly between groups. In conclusion, in this prospective cohort study, it was reported that patients who received boosting doses following the homologous mRNA vaccine scheme in SOT recipients developed a higher antibody response than those who completed the inactivated SARS-CoV-2 vaccine scheme and then received heterologous booster doses with mRNA vaccine. In our study, the detection of a higher titer of SARS-CoV-2 IgG antibody response in those who received mRNA vaccine alone compared to those who received inactivated vaccine alone is similar to the study of Dib et al (12).

Vályi-Nagy et al (13) compared the humoral and T-cell-mediated immune responses of the BBIBP-CorV (inactivated virus vaccine, Sinopharm) and BNT162b2 (mRNA-based vaccine, BionTech-Pfizer) vaccines against the SARS-CoV-2 virus. BBIBP-CorV vaccine has been found to cause levels of antireceptor binding domain (RBD) IgG as well as anti-spike protein (S) IgG and IgA antibodies in healthy individuals to be much lower than the antibody response developed after BNT162b2 vaccination, but still high in convalescent patients. The cumulative IFN γ -positive T cell response was only twofold higher in patients receiving BNT162b2 compared to patients receiving the BBIBP-CorV vaccine. On the other hand, BBIBP-CorV inactivated virus vaccine stimulates the T cell response targeting not only S but also nucleocapsid (N) and membrane (M) proteins. It has been reported that targeting only S protein epitopes may be advantageous compared to the mRNA vaccine, which stimulates the T cell response. In conclusion, BBIBP-CorV inactivated virus vaccine has been reported to be immunologically effective.

Tütüncü et al (14) investigated humoral responses following mRNA and inactivated virus vaccines in their prospective, cross-sectional study in patients with multiple sclerosis. In the study, SARS-CoV-2 IgG titers were evaluated in patients by chemiluminescent microparticle immunoassay. In the study, 852 (51%) patients received BNT162b2 vaccine, Coronavac TM vaccine was administered to 817 (48.9%) patients. BNT162b2 mRNA vaccine and Coronavac TM inactivated virus vaccines caused similar seropositivity; However, antibody titers were reported to be significantly higher in the BNT162b2 vaccine group than in the Coronavac TM vaccine group. No significant difference in COVID-19 infection rates was found among participants vaccinated with the BNT162b2 or Coronavac TM vaccines. In the study, mRNA and inactivated virus vaccines were reported to have equal long-term protection against COVID-19 infection, regardless of the antibody response.

Limitations

The study we present also has limitations. These are the lack of serial measurements after COVID-19 vaccination in CHB patients, the fact that SARS-CoV-2-specific T lymphocyte responses have not been evaluated, and the lack of opportunity to match CHD patients with health personnel in terms of age and gender.

Our study is interesting in that it is the first study in Turkey in which SARS-CoV-2 IgG antibody levels after vaccination with different vaccine types in CHB patients and different parameters such as age, gender, number of vaccines, active transmission of COVID-19 disease and treatment for CHB that may affect antibody level are analyzed.

Conclusion

In conclusion, CHB patients with Coronavac TM and BNT162b2 vaccines provide SARS-CoV-2 IgG antibody levels above the same cut-off value as the healthy control group, but since antibody levels are higher in both CHB patients and healthcare personnel who have been vaccinated with BNT162b2 alone or those who have received the heterologous vaccine with Coronavac TM+BNT162b2 if there are no contraindications, BNT162b2 vaccine may be preferred in CHB and health personnel.

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