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The Changes in The Anti-HBs Values Following COVID-19 Pneumonia

COVID-19 Pnömonisi Sonrası Anti-HBs Değerlerindeki Değişiklikler

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Abstract

Aim: We aimed to determine if there is a decrease in Anti-HBs titer below the protective value during Coronavirus-19 disease (COVID-19).

Material and Method: A prospective study was made of 67 patients who had positive Anti-HBs values checked in the last 1 year. Demographic data and the previous Anti-HBs values were collected from the patient files and the laboratory findings of new Anti-HBs titers checked after one months later following COVID-19 infection were compared with the previous ones.

Results: In the postcovid evaluation, a statistically significant decrease in the Anti-HBs levels of COVID-19 patients was determined with respect to previous values before COVID-19 infection ($p<0.001$).

Conclusion: In our study, we found that there was a statistically significant decrease in Anti-HBs levels after COVID-19 infection, but none of them were below protective Anti-HBs levels. As a result,we can say that despite the COVID-19 infection,protection against Hepatitis B continues in people with positive Hepatitis B antibodies.

Keywords: COVID-19, Anti-HBs , antibody level

Öz

Amaç: Coronavirus-19 hastalığı (COVID-19) sırasında Anti-HBs titresinin koruyucu değerin altına düşüp düşmediğini belirlemeyi amaçladık.

Gereç ve Yöntem: Son 1 yıl içinde pozitif Anti-HBs değerleri kontrol edilen 67 hasta ile prospektif bir çalışma yapıldı. Demografik veriler ve önceki Anti-HBs değerleri hasta dosyalarından toplandı ve COVID-19 enfeksiyonundan bir ay sonra kontrol edilen yeni Anti-HBs titrelerinin laboratuvar bulguları öncekilerle karşılaştırıldı.

Bulgular: COVID-19 sonrası yapılan değerlendirmede COVID-19 hastalarının Anti-HBs düzeylerinde COVID-19 enfeksiyonu öncesi önceki değerlere göre istatistiksel olarak anlamlı düşüş saptandı ($p<0.001$).

Sonuç: Çalışmamızda COVID-19 enfeksiyonu sonrası Anti-HBs düzeylerinde istatistiksel olarak anlamlı bir düşüş olduğunu ancak bunun koruyucu Anti-HBs düzeyinin altında olmadığını gördük. Sonuç olarak Hepatit B antikoru pozitif kişilerde COVID-19 enfeksiyonuna rağmen Hepatit B'ye karşı koruyuculuğun devam ettiğini söyleyebiliriz.

Anahtar Kelimeler: COVID-19, Anti-HBs, antikor düzeyi

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INTRODUCTION

Coronavirus-19 disease (COVID-19) is an infectious disease caused by a newly discovered. Coronavirus which was first seen in Wuhan. This new virus was identified in 2019, SARS-CoV-2, has caused a pandemic of respiratory illness and called COVID-19 pandemia. It spreads from person to person mainly by respiratory droplets produced when an infected person breaths, talks, laughs, sings, coughs or sneezes. This virus unfortunately can spread also by asymptomatic people. Larger droplets may fall to the ground in a few seconds, but tiny infectious particles can hang in the air and accumulate in closed places. COVID-19 is associated with diffuse lung damage. Most of the hospitalizations were due to Pneumonia. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.[1] Steroids may be required in patients who do not respond to antiviral therapy. Sometimes this treatment can be given in high doses. It is obvious that there is a possibility of activation of diseases that may exacerbate in immunosuppression in the body due to immunosuppression that may develop due to both the disease andthe drugs to be used. One of them is hepatitis B virus (HBV) infection. HBV infection remains a major global healthcare challenge.[2] Approximately 95% of individuals acutely infected in adulthood will spontaneouslyseroconvert and lose hepatitis b surface antigen (HBsAg).[2] It is well known that immunosuppression can stimulate replication of hepatitis B virus and precipitate severe flares of HBV infection. Fortunately, it can be largely prevented by prophylactic therapy with oral AntiHBV nucleosid/nucleotide analogues.[3] HBV is a heterotropic virus that has been shown in previous publications to be exacerbated under immunosuppression. An increasing number of therapeutic agents used are likely to interfere with the natural course of HBV infection. The risk of HBV reactivation is much lower in patients negative for HBsAg and positive for Hepatitis B Core antibody (Anti-HBc).[4] Anti-HBs is an antibody produced by the body against the surface antigen of the hepatitis B virus. Clinical interpretation of (+) Anti-HBs is recovery from acute or chronic infection and immunity following vaccination. HBsAg negative, AntiHBc positive serology usually indicative of past exposure to virus. Testing for HBV serology before initiating immunosuppressive medication is recommended by international societies.[2] Activation after exacerbation can lead to severe liver failure and can be mortal. Risk can be minimised through appropriate screening, monitoring and antiviral prophylaxis.

Therefore, the risk of hepatitis B activation should be estimated and precautions should be taken in necessary patients. The aim of our study is to investigate if there will be a decrease in Anti-HBs values and if so, will we need or not a booster vaccination following COVID-19 infection.

MATERIAL AND METHOD

Data collection

The research was designed as a prospective study and included 100 patients diagnosed and hospitalized with COVID-19 pneumonia in University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital between July 2021 and October 2021. Sixty seven of these 100 patients met the study criterias. The study inclusion criteria were as follows: 1-) Having given consent to participate in the study, 2-) Anti-HBs positive and HbsAg negative patients hospitalized with COVID-19 pneumonia, 3-) Not to be diagnosed with malignancy. 4-) To be over 18 years old.

Data were retrieved from the each patient with the diagnosis of COVID-19 pneumonia, in respect of medical history, age and sex; the laboratory data including Anti-HBs and Anti-HBc IgG values checked for nonspecific reasons in the last 1 year before internationalization of these patients were taken from medical records. It means Anti-HBs titers were checked at least once before and after COVID-19 infection. During the hospitalizations,we also recorded the laboratory findings like fibrinogen, ferritin, d-dimer, complete blood count including lymphocyte count, C-reactive protein (CRP), procalcitonin,internalised normalised ratio (INR), glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumine, total bilirubine (T.bil), direct bilirubine (D.bil) and the duration of hospitalization time, given treatments and their duration, if any, cases of referral to the intensive care unit and discharge information.

When the patients who were discharged after hospitalization with covid -19 pneumonia came to the outpatient clinic control one month later, blood was taken from each patient in a biochemistry tube and centrifuged, and their blood serum was placed in 2 ml eppendorfs and stored in the refrigerator at -80 degrees in the laboratory of our hospital until the end of the study. When sufficient number of patients was reached, blood serums were taken out of the refrigerator which was at -80 degrees and Anti-HBs measurements were made. Anti-HBs levels were examined by using the Roche Hitachi Cobas 8000 modular analyzer system (Roche Diagnostics, Germany).

To conduct this study, ethical approval was granted by the Local Ethics Committee (reg: E- 48670771- 514.10). Prior to the study, informed consent was obtained from all patients.

Statistical Analysis

Normality control of continuous variables was evaluated with the Shapiro Wilk test. Non-parametric methods were chosen in the relevant analyzes since Anti-HBs values did not conform to the normal distribution. The Wilcoxon test was used to compare the 1st and 2nd Anti-HBs values, the Mann Whitney U test was used to compare the two independent groups, and the Spearman Rho correlation coefficient was calculated while examining the linear relationship with continuous variables. Data analysis was done in SPSS 21 program and $p<0.05$ was considered statistically significant.

RESULTS

One hundred patients who had previous Anti-HBs positivity in the last one year, with the diagnosis of COVID-19 pneumonia have been evaluated. A total of 67 adult patients who met the study criteria were included in the study. The patients comprimised 41 males (61.2%) and 26 females (38.8%) with a mean age of 58.3±18.4 years. Summary of the demographic and laboratory findings of the patients are shown in **Table 1**. Total AntiHBc was positive in 43 (64.2%) of the patients. 24 (35.8%) patients have not received immunosuppressive treatment. 43 (64.2%) Patients have received immunosuppressive treatment. The decrease in Anti-HBs titers after COVID-19 infection was statistically significant (p<0.001). Anti-HBs titers before and after the COVID-19 infection are shown in **Table 2** and **Figure 1**.

The decrease in Anti-HBs values was higher in men compared to women (p=0.002). The difference in Anti-HBs levels between male and female genders is shown in **Table 3**. When compared with other laboratory parameters and length of stay, it was observed that the albümin level had a significant effect on the difference in Anti-HBs values before and after COVID-19 infection. As albumin values decrease, an increase in Anti-HBs difference is observed (r:-0.273 p=0.025). The findings are shown in **Table 4**. In addition, when the difference of Anti-HBs values before and after COVID-19 infection was evaluated according to the treatment applied, no significant relationship was found. Anti-HBs difference according to treatment is shown with **Table 5**. Among our 67 patients, 4 (6%) patients have postcovid Anti-HBs levels of less than 20 miu/mL. These values were near to the lower protective limit of Anti-HBs level. The 9 patients who had Anti-HBs levels of 1000 miu/mL before COVID-19 infection, have also postCOVID Anti-HBs levels of 1000 except one patient whose Anti-HBs level has decreased 57.5%. Of these 9 patients only one has antiHBc IgG (+) an the other 8 have Anti-HBc IgG (-). There were not a statistically significant difference between the Anti-HBc IgG positive and negative groups with respect to the amount of decreasement in Anti-HBs levels.

Table 2: Anti-HBs values before and after COVID-19 infection

	Mean±SD	Median [IQR]	Min-Max	P value
1.Anti-HBs	304.1±329.2	149 [61-427.8]	13.7-1000	<0.001*
2.Anti-HBs	263.2±312.2	118 [43.7-394]	10.9-1000	
Anti-HBs difference	40.9±104.7	13.3 [0-53]	-275-700	

p: Wilcoxon test, *: refers to significant values, 1.Anti-HBs : Anti-HBs level before COVID-19 infection, 2. Anti-HBs : Anti-HBs level after COVID-19 infection.

Table 3: Anti-HBs difference between male and female genders

Anti-HBs difference	Mean±SD	Median [IQR]	Min-Max	P Value
Female	-2.7±84	4.38 [-15.3-21]	-275-202	0.002*
Male	68.5±107.9	27 [6.3-114]	-90.3-425	

p: Mann Whitney U test, *: refers to significant values

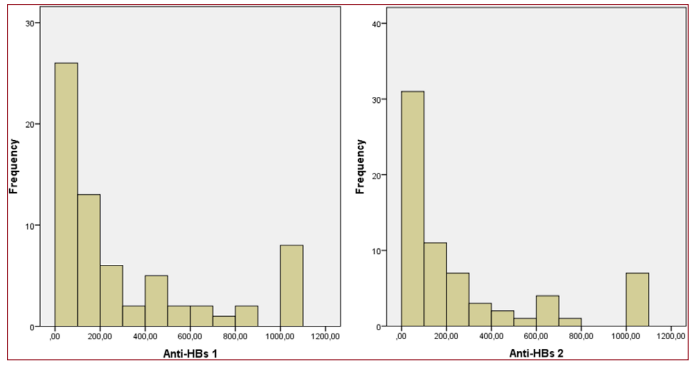

Figure 1: Anti-HBs values before and after COVID-19 infection.

Table 1: Summary of the demographic and laboratory findings of the patients

	Mean±SD	Median [IQR]	Min-Max
Age (year)	58.3±18.4	58 [44-74]	21-92
Albumin (g/dL)	3.4±0.5	3.2 [3-3.8]	2.2-4.2
Total bilirubin (mg/dL)	0.6±0.4	0.6 [0.3-0.9]	0-2.1
GGT (U/L)	69.5±56.7	53 [36.5-87.5]	14-419
WBC (µl/mL)	7573.6±4058.2	7000 [4700-9400]	1200-21900
Hb (g/dL)	12.5±2.6	13 [11.2-13.9]	7.7-17
Trombosit (/mm³)	217761.2±98937.1	201000 [144000-289000]	25000-486000
CRP (mg/L)	100.7±73.1	94 [26.5-155.8]	0.7-271
Procalcitonin (ng/mL)	0.5±1.4	0.08 [0-0.3]	0.01-7.6
D-Dimer (ng/mL)	1147.7±1178	800 [320-1500]	60-5800
Ferritin (ml/ng)	835.8±758.1	670 [231-1203]	34-3243
Fibrinogen (mg/dL)	563.5±189.1	583 [462-694]	170-1012
INR	1±0.3	1 [0.9-1.1]	0.2-3
Glucose (mg/dL)	133.1±65.6	111 [88-155]	71-355
ALT (U/L)	39.6±37.9	24 [16-52]	3-187
Creatinin (mg/dL)	1.3±1.6	0.8 [0.7-1.1]	0.2-8.3
Lymphocyte count (10^9/L)	849.1±520.2	800 [500-1060]	100-3000
Hospitalization (day)	12.8±9.1	11 [7-17]	3-57

GGT: Gamma-glutamyl transferase, WBC: White Blood Cell. Hb:hemoglobin, CRP: C-reactive protein, INR: International normalized ratio, ALT: Alanine aminotransferase

Table 4: The effect of laboratory parameters and length of stay on Anti-HBs difference

Anti-HBs difference	r	p
Age	0.24	0.05
Anti HBc IgG (s/co)	-0.203	0.1
Albumin (g/dL)	-0.273*	0.025*
Total bilirubin (mg/dL)	0.087	0.486
GGT (U/L)	0.171	0.171
WBC (µl/mL)	-0.006	0.962
Hb (g/dL)	0.028	0.823
Thrombocyte	-0.01	0.935
CRP(mg/L)	-0.027	0.831
Procalcitonin (ng/mL)	-0.091	0.466
D-Dimer (ng/mL)	0.219	0.074
Ferritin (ml/ng)	-0.011	0.931
Fibrinogen (mg/dL)	0.115	0.36
INR	0.035	0.78
Glucose (mg/dL)	-0.047	0.708
ALT (U/L)	0.081	0.514
Creatinin (mg/dL)	0.015	0.903
Lymphocyte count(10^9/L)	-0.048	0.702
Hospitalization (day)	0.239	0.051

p: Spearman Rho Correlation, *: refers to significant values, GGT: Gamma-glutamyl transferase, WBC: White Blood Cell, Hb: hemoglobin, CRP: C-reactive protein, INR: International normalized ratio, ALT: Alanine aminotransferase

Table 5: The effect of the treatment applied in COVID-19 patients on the level of Anti-HBs difference

	Anti-HBs difference			
	Mean±SD	Median [IQR]	Min-Max	P Value
Anti-HBc IgG				
Present	43.9±95.2	21.3 [4.5-90]	-275-267.42	0.099
Absent	35.5±121.8	6.6 [0-35.2]	-157-425	
Immunoplasma				
Present	34.6±49.2	19.7 [1.82-6]	-6.3-129	0.822
Absent	41.5±108.8	13.3 [0-60.5]	-275-425	
Methylprednisolone				
Present	33.6±91.1	12.3 [0-32.5]	-157-267.42	0.425
Absent	45.5±113.3	21.3 [0-71.5]	-275-425	
Pulse steroid				
Present	33.7±61.9	12.1 [0-65.5]	-65-189	0.79
Absent	43.3±116.1	16.4 [0-56.7]	-275-425	
Tocilizumab				
Present	79.1±95.9	36 [12.4-]	12.4-189	0.296
Absent	39.1±105.4	12.9 [0-51.5]	-275-425	
Macrolide				
Present	40±91.3	18 [0-67.9]	-157-364	0.661
Absent	42.5±127.3	7.4 [0-32.4]	-275-425	
Ceftriaxone				
Present	43.2±115.8	13.7 [3.18-69.5]	-275-425	0.616
Absent	35±71.4	13.3 [0-44]	-50.4-266	
Piperacillin tazobactam				
Present	16.9±127.9	12.6 [0-41]	-275-266	0.647
Absent	45.6±100.2	16.4 [0-64.2]	-157-425	
Dexamethasone				
Present	62.8±108.5	33.2 [5.05-108]	-90.3-364	0.184
Absent	32.2±103	12.5 [0-34.8]	-275-425	
Meropenem				
Present	13±0.5	13 [12.6-]	12.6-13.3	0.985
Absent	41.8±106.2	14.7 [0-60.5]	-275-425	

p: Mann Whitney U test

DISCUSSION

In the current medical literature there was not any information about the effect of COVID-19 infection itself on Anti-HBs levels. In our research the Anti-HBs levels of the patients with COVID-19 infection were decreased significantly (p<0.001). No significant difference was found between immunosuppressive treatment or the use of any drug and the significant decrease in Anti-HBs values. We thought that the decrease in Anti-HBs values was secondary to the COVID-19 infection itself. In the prospective study of Sergio Rodriguez et al they analysed the risk of HBV reactivation in patients with severe COVID-19 undergoing immunosuppressive therapy. By supporting our findings, they showed that the risk of HBV reactivation in patients with severe COVID-19 undergoing immunosuppressive treatment is low.[5]

Perillo et al. said that steroids decrease specific T-cell response and increases the virus replication and the risk of infection is directly proportional to the duration and dose of the steroid.[6] In our research we have not seen any effect of duration or amount of steroids given on Anti-HBs levels. Demet Yalcın Kehribar et al. studied the impact of tumor necrosis factor alpha antagonist treatment on antibody titer of hepatitis B surface antigen and they showed that there was a statistically significant decrease in the Anti-HBs levels after immunosuppressive treatment also they observed that in a small number of patients the level of Anti-HBs decreased to a risky level.[7] Therefore they suggested booster vaccination against hepatitis B virus in these patients. In our study also similar to their research there was not any reactivation of hepatitis B virus. The study of Yuri Cho et al. was named as the titer of Anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patients with non-Hodgkin's lymphoma.[8] They showed that 8 cases of 108 resolved hepatitis B patients had HBV reactivation with Anti-HBs titers less than 100 mıu/mL. They said that high baseline Anti-HBs titers prevented HBV reactivation and suggested antiviral prophylaxis should be considered according to Anti-HBs titer. In another study of Tamori et al. they also showed that there was a significantly decrease in Anti-HBs levels after anti-TNF alpha treatment.[9] Vassilopoulos et al. had similar results with Tamori et al.[10] Cam et al. showed that protective AntiHBs levels remarkably altered after chemotherapy in the pediatric oncology cases.[11] Francois-Xaiver et al.said that monitoring the AntiHBs level remains necessary as it has been reported that only 42% of HIV infected responders kept their protective titers 13-18 months after their last dose of vaccine.[12,13] Marinaki et al. emphasized that immunosuppression is intimately associated with increased viral replication.[14-20] In our study,the decrease in Anti-HBs values was higher in men compared to women. Although there is no information in the literatüre on this subject,it was thought that this situation may be due to hormonal differences between 2 genders because sex hormones may have an affect on immunity; in women, estrogen reduces pro-inflammatory signals.[21] Kim S et al.

emphasized that although the effect of gender on immunity is well known,more studies are needed on this subject.[22] Irelli et al. said that androgens suppress the activity of immune cells and estradiol improves immune responses; estrogens stimulate plasma cells to produce immunoglobulins.[23] Also there is a greater oxidative stress in men due to reduced activity of antioxidants.[24] The strength of immune responses differ between women and men; women are in general able to mount a more vigorous immune response to infections and vaccinations.Common biological pathways leading to immune activation are regulated by sex linked factors.[25] Guglielmo et al. expressed that hepatitis B virus represents a leading cause of acute or chronic liver disease so the goal is to assure individual protection, also providing booster doses when needed after many years following the primary vaccination but we suggest that after viral infections maybe we should not wait untill late years and we may need early booster vaccinations.[26]

CONCLUSION

To sum up; in our research we observed that the Anti-HBs levels of the patients with COVID-19 infection decreased significantly; we haven't seen any reactivation. At beginning of our research we had wondered which Anti-HBs levels were more likely to decrease after COVID-19 infection but we could not see a cut off value for Anti-HBs level. In non of the patients, despite the decrease in Anti-HBs levels, we have not seen a decrease of Anti-HBs levels to a risky level below the protective value. For this reason, we thought that intermittent booster doses of HBV vaccination were not necessary in our patients. On the other hand, in some of the patients there were Anti-HBs decrease near to the lower limit of protective Anti-HBs values, therefore, if we can search more patients maybe we would find more decreasements below the protective Anti-HBs levels. Therefore further research is needed to validate this with more patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study was granted from University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital Ethics Committee for Clinical Studies in July 2021 (reg: E- 48670771- 514.10).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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