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Research Article

Is Post-COVID 19 Vaccination Antibody Level Related to Happiness and Stress Hormones?

Cihat Ucar[1], Faruk Disli[2], Tugce Atcali[3], Sedat Yildiz[2]

[1]Malatya Turgut Özal University, Faculty of Medicine, Department of Physiology, Malatya, Türkiye
[2]İnönü University, Faculty of Medicine, Department of Physiology, Malatya, Türkiye
[3]Bingöl üniversity, Faculty of Veterinary Medicine, Department of Physiology, Bingöl, Türkiye

Abstract

Aim: The level of antibody production in those vaccinated against coronavirus can be affected by many different situations. There is an important balance between immune response, stress and emotional state. However, it is not known how this situation affects antibody production after vaccination. This study aimed to investigate the correlation between the antibody response induced by the COVID-19 vaccine and the hormones cortisol, a marker of the stress axis, and serotonin, a marker of happiness.
Material and Method: Serum cortisol and serotonin levels were analyzed in those who tested positive (n=40) and negative (n=40) for Anti-SARS CoV-2 IgG induced by vaccination. Anti-SARS CoV 2 IgG, cortisol, and serotonin levels were determined by using the ELISA method. The data were compared using the Mann-Whitney U test. The value of $p<0.05$ was considered as statistically significant.
Results: Cortisol level (42.2±26.2 ng/ml) and serotonin level (414±246 ng/ml) were determined in subjects who tested positive for Anti-SARS CoV-2 IgG, while cortisol level (45.1±34.5 ng/ml) and serotonin level (372±209 ng/ml) were determined in subjects who tested negative for Anti-SARS CoV-2 IgG. There was no statistical difference or correlation between cortisol and serotonin levels in those with positive and negative levels of Anti-SARS CoV-2 IgG ($p>0.05$).
Conclusion: Consequently, no effect of the stress parameter cortisol and the happiness parameter serotonin, was found in vaccine-induced immunization. It is considered that the different antibody responses in individuals may vary depending on other factors.

Keywords: COVID 19 vaccination, anti-SARS CoV 2 IgG, cortisol, serotonin

INTRODUCTION

In December 2019, a group of patients in Wuhan, Hubei Province, China, were identified with pneumonia of unknown cause. On 7 January, 2020, the Chinese Centers for Disease Control and Prevention identified a new beta-coronavirus in lower respiratory tract samples from patients with pneumonia (1). This novel coronavirus was later named "severe acute respiratory syndrome coronavirus-2". (SARS-CoV-2). Unlike other coronavirus outbreaks, the virus is easily transmitted from person to person, primarily through inhalation, droplets, respiratory secretions, and direct contact. From the first day of its spread until 17 August 2021, the virus has infected more than 273 million people and caused 5.3 million fatalities (2).

A strong immunity develops after the COVID-19 infection. This results in the formation of virus-specific antibodies. Vaccination is recommended for the formation of immunity in those, who have not been infected, and considered the only solution for disease prevention. Therefore, a better understanding of the development of humoral immunity in response to infection in individuals who have been exposed to disease or who have been vaccinated is required. This is because the development of an antibody response is affected by many factors. When the studies are reviewed, it is observed that the antibody response in individuals who have survived the disease or who have been vaccinated is different (3-5). It has been reported that an increase in Anti-SARS CoV-2 immunoglobulin-G (IgG) is proportional to the rise in the severity of the disease in infected individuals, while Anti-SARS CoV-2 IgG is found to a lesser extent in asymptomatic/mild individuals and those who have been treated with immunosuppressive

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Corresponding Author: Cihat Ucar, Malatya Turgut Özal University, Faculty of Medicine, Department of Physiology, Malatya, Türkiye
E-mail: ucarcht@gmail.com

medications (3,6). Different studies have also reported that antibody responses differ depending on age (7), gender (8), and hormones (9,10). Antibody responses have been found to be different between adults and children (11,12). Not only are different antibody responses evoked after SARS-CoV-2 infection, but different antibody responses are also elicited in vaccinated individuals who have not been infected. Vaccines approved by the World Health Organization are administered all over the world. In Türkiye, mRNA-based and inactivated vaccine forms are available. Vaccines have the ability to produce antibodies through different mechanisms. This difference may induce changes in the formation of antibodies in humans (4). Studies have shown that neutralizing antibodies against COVID-19 are produced after vaccination. However, it is not yet known how much these neutralizing antibodies are produced in each individual and how protective they are.

There is an important balance between the immune system, stress, and emotional state. A study reported that psychological stress is vital to the severity and recurrence of acute respiratory diseases (13). Long-term increases in stress hormones can trigger inflammatory responses by suppressing the cellular and humoral immune systems (14). Recent studies have reported differences in the immune responses of COVID-19 patients (15). Stress leads to activating the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) (16). As a result of HPA activation, the release of cortisol as an end product in the bloodstream increases (16). There is a bidirectional correlation between emotional state and serotonin. Increased serotonin hormone may affect the central nervous system and autonomic nervous system, leading to immune modulation (17). Peripheral serotonin is a potent immune modulator and affects various immune cells through its receptors (18). The hormone serotonin directly affects B lymphocytes through its receptors on B lymphocytes (18). However, the roles of serotonin hormone in immune cell functions or the formation of the immune response are not yet known.

This study aimed to investigate the correlation between the antibody response induced by the COVID-19 vaccine and the hormones cortisol, a marker of the stress axis, and serotonin, a marker of happiness.

MATERIAL AND METHOD

Study Design and Participants

The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and approved by the scientific ethics committee (Protocol# 2022/3161). All written consent was obtained from the participants. 80 participants were included in the study. All participants were vaccinated with Sinovac/CoronaVac in two doses at 21-day intervals. Anti-SARS CoV-2 IgG was measured from serum samples collected 21 days after the second dose. Two groups were formed: 40 people who tested positive for antibodies (antibody positive) and 40 people who tested negative for antibodies (antibody negative). Cortisol and serotonin were then measured in the serum of all participants in both groups.

Enzyme-Linked Immunosorbent Assay for Anti-SARS CoV-2 IgG

For the detection of anti-SARS-CoV-2 IgG, a commercial enzyme-linked immunoassay (ELISA) test (QuantiCOR, Y Immunotek A.S.) was used. This test was approved for quantification of COVID 19 IgG antibodies in human sera by the Ministry of Health of Türkiye, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products, which follows the criteria outlined by the World Health Organization (WHO). Optical density (OD) ratios were calculated by dividing the OD at 450 nm by the OD of the cut-off included in the kit. The calculated cut-off index (COI) was used as a relative measure for the titer of antibodies in serum. For IgG response, a COI of >1.0 was considered positive (19). Samples from both groups were studied on the same test plate.

Enzyme-Linked Immunosorbent Assay for Cortisol

Following thawing, samples were centrifuged at 4000 g for 10 min and the supernatant was used for ELISA analyses as reported by Ozgocer et al. (20). Samples were diluted 5x with assay buffer and assayed in duplicate. Briefly, cortisol-BSA stock solution was diluted with carbonate buffer and added to a 96-well micro titer plate at 200 µL/well. Following incubation overnight at +4°C and they were washed 5 times with wash buffer using eight-channel pipette. Binding sites not occupied by the coating antigen were blocked by the blocking buffer (200 µL/well) for 2 h at 37°C. Following washing steps (5 times), standard solutions or samples (40 µL/well) and diluted primer antibody (antiserum) (40 µL/well) were added in duplicate and incubated at 37°C for 45 min. Following washing 5 times, biotinylated anti-rabbit antibody was added (100 µL/well) and the plate was incubated at 37°C for 30 min. The plate was washed 5 times and the streptavidin peroxidase solution (100 µL/well) was added and the plate was incubated for 15 min at +4°C. Then, the plate was washed again for 5 times and the substrate solution (150 µL/well) was added and incubated in dark for 10 min. Following incubation, stop solution (50 µL/well) was added and the absorbance was measured at 450 nm using a microplate reader. Samples from both groups were studied on the same test plate.

Enzyme-Linked Immunosorbent Assay for Serotonin

Serotonin was measured using a test kit from DRG. Before running the test, serum was acylated and the samples were prepared. To do this, 25 ul of each of serum, control, and standards were added into 1.5 ml Eppendorf tubes, and 500 ul of acylation buffer and 25 ul of acylation reagent were added into them and incubated for 15 minutes at room temperature.

Pipette 25 ul of the acylated standartds, controls and samples into the appropirate wells of the serotonin microtiters strips. Pipette 100 ul of the serotonin antiserum into all wells. Incubate 1 h at room temperate. Dsicard the contents of the wells. Wash the plate 3 x by adding 300 ul of wash buffer, discarding the content and blotting dry each time by tapping the inverted olate on absorbent material. Pipette 100 ul of the cojugate into all wells and incubate 15 minute at room temperate. Discard the contents of the wells. Wash the plate 3 x by adding 300 ul wash buffer, discarding the content and blotting dry each time by tapping the inverted olate on absorbent material. Pipette 100 ul of the substrate into all wells and incubate 15 minute at room temperate (avoid exposure to direct sunlight). Add 100 ul of the stop solution to each well. Read the absorbance of the solution in the wells within 10 minutes, using a microplate reader set to 450 nm. Samples from both groups were studied on the same test plate.

Statistical Analysis

All statistical analyses were conducted using Minitab program (MINITAB 19, PA, USA). The normal distribution of the data was evaluated with the Normality Test. Mann Whitney U test was used to compare groups. The correlations were calculated with Spearman Rho coefficient. The data were presented as mean±standard deviation. p<0.05 was considered as statistically significant.

RESULTS

Table 1 presents the results of Anti-SARS CoV-2 IgG measured in those who were vaccinated with the COVID-19 vaccine and the cortisol and serotonin levels in the groups that tested positive and negative for IgG. There was no statistical difference in cortisol and serotonin levels in the groups that tested positive and negative for Anti-SARS CoV-2 IgG (p>0.05).

Table 2 shows the correlations between IgG, cortisol, and serotonin levels in the group that tested positive for Anti-SARS CoV-2 IgG. Table 3 presents the correlations between IgG, cortisol, and serotonin levels in the group that tested negative for Anti-SARS CoV-2 IgG. There was no statistically significant correlation between Anti-SARS CoV-2 IgG, cortisol, and serotonin levels in both groups (p>0.05).

Table 1. Levels of anti SARS-CoV-2 IgG, cortisol and serotonin in participant

	COVID 19 Ab (+) (n=40)	COVID 19 Ab (-) (n=40)	p value
Anti-SARS-CoV-2 IgG	6.18±4.05	0.65±0.02	0.000
Cortisol (ng/ml)	42.23±26.22	45.16±34.53	0.642
Serotonin (ng/ml)	414±246	372.6±209.3	0.433

Ab titer: antibody index, (serum/cutoff ratio) x10; positive >1.0. The data represents mean±standard deviation

Table 2. Correlations between Anti-SARS-CoV-2 IgG, cortisol and serotonin in COVID-19 Ab (+)

Variables	Cortisol (ng/ml)	Serotonin (ng/ml)
Anti-SARS-CoV-2 IgG	0.037 >0.05	0.244 >0.05
Cortisol (ng/ml)		-0.117 >0.05

In each cell, upper value is R-squared, lower values is p

Table 3. Correlations between Anti-SARS-CoV-2 IgG, cortisol and serotonin in COVID-19 (-)

Variables	Cortisol (ng/ml)	Serotonin (ng/ml)
Anti-SARS-CoV-2 IgG	0.058 >0.05	0.187 >0.05
Cortisol (ng/ml)		-0.120 >0.05

In each cell, upper value is R-squared, lower values is p

DISCUSSION

In this study cortisol and serotonin hormones were measured in those who were not infected with COVID-19 and who tested positive and negative for anti-SARS CoV 2 IgG with two doses of the Sinovac vaccine. Correlations between all parameters were also checked. No statistically significant difference was found between cortisol and serotonin levels in the subjects who tested positive for COVID-19 IgG and those who tested negative. No correlation was found between anti-SARS CoV 2 IgG, cortisol, and serotonin in both groups.

The COVID-19 pandemic has raised panic and anxiety all over the world. Our lifestyle and habits have dramatically changed. Unlike other viral infections, the COVID-19 pandemic has been depicted by the media as a peculiar hazard that heightens fear, tension, and anxiety. Such circumstances have profoundly affected both the immune system and the neuroendocrine system. The central nervous system, the endocrine system, and the immune system are interrelated. It is widely recognized that stress impairs the immune system (21). Evidence shows that high levels of chronic psychological stress reduce antibody responses to vaccination (22,23). Besides chronic stress, a lifestyle that fosters negative personality traits has also been associated with poor antibody responses in young and healthy individuals (24,25). Acute stress, on the other hand, has been reported to increase antibody responses. A pandemic such as COVID-19 increases anxiety in humans, which would inevitably have an effect on the generation of antibody responses. No correlation was detected between the antibody responses induced by the vaccine, and cortisol, which is considered a stress parameter in this study. Therefore, the correlation between stress and antibody responses seems to depend on other factors. Even if the vaccine was administered, the absence of an antibody response was not found to be correlated with cortisol.

Serotonin is associated with the state of happiness and is used as an anti-depressant (18). However, the correlation between serotonin and antibody responses has not yet been clarified. There is a serotonin receptor on B lymphocytes responsible for the antibody response (18). Therefore, there may be a possible correlation between serotonin and antibody responses. However, the literature includes no studies on the correlation between serotonin and antibody responses in humans. There are a few studies on animals in which serotonin does not affect (17), reduces (26), or increases the antibody response (27). The effect of the fear and anxious state induced by the COVID-19 pandemic on the antibody response has not been known. Therefore, this study analyzed the serotonin levels in individuals who were vaccinated but had different antibody levels. However, no difference was found in serotonin levels.

CONCLUSION

Consequently, no effect of the stress parameter cortisol and the happiness parameter serotonin on vaccine-induced immunization was found. It is considered that different antibody responses in individuals may vary depending on other factors.

Strength and limitation of the study: The time of collection of serum samples could not be standardized for all participants.

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

Ethical approval: Ethical approval number 2022/3161 was received by İnönü University Scientific Research and Publication Ethics Committee.

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