ANALYSIS OF DIFFERENCES IN THE CONCENTRATION OF ANTI-SARS-COV-2 ANTIBODIES IN THE COURSE OF COVID-19 DEPENDING ON DISEASE SEVERITY, SEX, AGE, AND VACCINATION STATUS

Analiza różnic w stężeniu przeciwciał przeciw SARS-CoV-2 w przebiegu COVID-19 w zależności od ciężkości choroby, płci, wieku i statusu szczepienia

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Abstract

Introduction and objective: The role of immunoglobulin G antibodies in combating SARS-CoV-2 infection, modulation of COVID-19 disease severity, and persistence of humoral response after primary infection and vaccination is unclear. This study aimed to evaluate the role of antibodies in limiting the infection, modulating disease severity, and determining the durability of the immune response depending on the clinical status of patients, their age, sex, and vaccination status. **Material and methods:** The study involved 156 patients, 99 men and 57 women, aged 58.3 ± 12.5 years old, hospitalised for pneumonia in the course of COVID-19, with infection confirmed by real-time polymerase chain reaction test. The concentration of anti-SARS-CoV-2 IgG antibodies was tested at 3, 6, and 9 months from the day of hospitalisation. **Results:** The concentration of anti-SARS-CoV-2 IgG antibodies in patients with severe COVID-19 was higher compared to the group of patients with mild to moderate disease. The level of anti-SARS-CoV-2 IgG antibodies was comparable in men and women. In patients over 60 years of age, a lower concentration of antibodies was observed than in patients under 60 years of age. In the vaccinated group, the level of antibodies was higher than in the unvaccinated group. **Conclusions:** The study findings showed that the concentration of IgG anti-SARS-CoV-2 antibodies was not a parameter dependent on the sex of the patients, but rather on the severity of the disease and the age of the patients and their vaccination status.

Streszczenie

Wstęp i cel pracy: Rola immunoglobuliny G w zwalczaniu ostrej niewydolności oddechowej wywołanej zakażeniem SARS-CoV-2, modulacji ciężkości COVID-19 i utrzymywaniu odpowiedzi humoralnej po pierwotnym zakażeniu i szczepieniu nie jest jasna. Celem pracy była ocena roli przeciwciał w ograniczaniu zakażenia, modulacji ciężkości choroby i odpowiedzi immunologicznej w zależności od stanu klinicznego pacjentów, ich wieku, płci i statusu szczepienia. **Materiał i metody:** Badaniem objęto 156 pacjentów, w tym 99 mężczyzn i 57 kobiet, w wieku 58,3 ± 12,5 roku, hospitalizowanych z powodu zapalenia płuc w przebiegu COVID-19, z zakażeniem potwierdzonym testem łańcuchowej reakcji polimerazy w czasie rzeczywistym. Stężenie przeciwciał IgG przeciw SARS-CoV-2 badano w miesiącach 3., 6. i 9. od dnia hospitalizacji. **Wyniki:** Stężenie przeciwciał IgG przeciwko SARS-CoV-2 u pacjentów z ciężką postacią COVID-19 było wyższe w porównaniu z grupą pacjentów z łagodną i umiarkowaną postacią choroby. Stężenie przeciwciał IgG przeciw SARS-CoV-2 było porównywalne u mężczyzn i kobiet. U pacjentów powyżej 60. roku życia obserwowano niższe stężenie przeciwciał niż u pacjentów poniżej 60. roku życia. W grupie zaszczepionej stężenie przeciwciał było wyższe niż w grupie niezaszczepionej. **Wnioski:** Przeprowadzone badania wykazały, że stężenie przeciwciał IgG przeciw SARS-CoV-2 nie jest parametrem zależnym od płci, ale raczej od ciężkości choroby, wieku pacjentów i ich statusu szczepienia.

Keywords: vaccination; antibodies; SARS-CoV-2

Słowa kluczowe: szczepienie; przeciwciała; SARS-CoV-2

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Introduction

The first case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was officially confirmed on 1 December 2019 in Wuhan, China, [1]. The rapidly spreading virus caused COVID-19 disease in 757,264,511 individual cases, of which 6,850,594 were fatal [1]. The introduction of vaccination (13,220,848,592 vaccinated individuals [2]), as well as the rise of population immunity developed through infection, made it possible to eventually slow down the pandemic. Nevertheless, complete eradication of SARS-CoV-2 was not possible. It is believed that the virus, similarly to other coronaviruses or influenza viruses, will cause recurrent outbreaks of varying morbidity. These fluctuations in prevalence depend on many factors, such as the adoption of restrictions by affected communities and effective epidemiological surveillance. One of the indicators of population immunity to infectious diseases is the assessment of the titre of the immunoglobulin G (IgG) antibodies. In the case of SARS-CoV-2, the available data is insufficient to unequivocally state that the analysis of the concentration of anti-SARS-CoV-2 antibodies is directly associated with the acquisition of natural and post-vaccination immunity. Current data on the role of antibodies in combating infections, modulation of COVID-19 severity, and the persistence of humoral response after primary infection and vaccination is either limited or controversial [3–5].

Most individuals infected with SARS-CoV-2 develop antibodies against spike (S) and nucleocapsid (N) proteins, which are also used in clinical serological tests [6]. The spike protein is an important target for neutralising antibodies. The combination of these antibodies with the S protein of the virus can effectively prevent the virus from entering the host cells [7, 8]. Seroconversion for the IgM antibodies usually occurs within 5 days of the onset of symptoms, and seroconversion for the IgG antibodies – within 7 days. Depending on the method used and individual variability, seroconversion can be observed after a median time of 10–13 days from the onset of symptoms in the case of IgM antibodies and 12–14 days in the case of IgG antibodies [9]. Maximum seroconversion occurs within 2–3 weeks for IgM antibodies, 3–6 weeks for IgG antibodies, and 2 weeks for all antibodies. While IgM antibodies tend to disappear at around 6–7 weeks, high IgG seropositivity is observed at the same time. Reports on the persistence of SARS-CoV-2 antibody titres are not fully consistent, with some finding a rapid decline in virus-specific IgG antibodies approximately 3 months after infection, and others highlighting stable titres detected more than a few weeks or even months post infection [10–14].

The concentrations and chronological order of appearance of IgM and IgG antibodies are highly variable, which provides the basis and justification for the parallel detection of both these antibodies. The time of seroconversion following stimulation of humoral response by the administration of the vaccine seems to coincide with the natural process of appearance of anti-SARS-CoV-2 antibodies after infection. From the currently available studies, it can be concluded that messenger Ribonucleic Acid (mRNA) vaccines induce a higher titre of IgG antibodies after 1 and 2 doses compared to traditional vaccines [15–17]. Nevertheless, this data does not indicate the greater effectiveness of mRNA vaccines. The present study is an analysis of anti-SARS-CoV-2 antibody concentrations in individuals with COVID-19 during their hospitalisation and convalescence. The study was conducted to evaluate the role of antibodies in limiting the infection, modulating the disease severity, and determining the durability of the immune response depending on the clinical status of patients, their age, sex, and vaccination status.

Material and methods

This study involved 156 individuals, including 99 males and 57 females, aged 58.3 ± 12.5 years old, diagnosed with pneumonia in the course of COVID-19, with or without symptoms of acute respiratory failure, and hospitalised at the Military Institute of Medicine – National Research Institute (MIM-NRI Poland) between January and November 2021.

Patients with COVID-19 who met the following criteria were included in the study:

- presence of SARS-CoV-2 infection confirmed with real-time polymerase chain reaction (PCR);
- pneumonia confirmed with computed tomography;
- passive oxygen therapy required;
- high-flow oxygen therapy or ventilator therapy required.

All the individuals were informed about the purpose of the study and gave their informed consent to participate. The consent of the local Bioethics Committee was also obtained. An additional study group was established, consisting of 67 individuals vaccinated against COVID-19 after their symptoms completely subsided.

Peripheral blood samples of 8 mL per draw were collected by venipuncture into the cubital fossa at 3, 6, and 9 months from the day of initial hospitalisation. The blood samples were centrifuged at 3,000 rpm for 5 minutes at room temperature, and the obtained serum was frozen and stored at -25^{0}C. The determination of anti-SARS-CoV-2 antibodies was performed using an IgG and IgM antibody quantification kit by ELISA. The determination of the antibody titre was performed in serum using the COVID-19 ELISA IgM + IgA and COVID-19 ELISA IgG kits by Vircell Microbiologists (Spain) on the Dynex Magellan Biosciences sys-

tem. The test was targeting anti-SARS-CoV-2 antibodies against S protein. The results were read using DS-Matrix 1.40.3. Each subject had the presence of the SARS CoV-2 virus confirmed by the Real-Time PCR test using GeneFinder™ COVID-19 Plus RealAmp Kit (Korea) reagents on the Bioer LineGene 9600 Plus system.

Statistics

The data obtained during the study were of three types: range (age, time points of the study), ordinal (assessment of the clinical condition), and nominal (sex, vaccination status – vaccinated or unvaccinated). Because the study groups were markedly unequal in size, the statistical analysis was performed with the Wilcoxon test. Differences between the variables were considered significant when the level of significance *p* was lower than 1-α = 0.05 for the obtained test value.

Results

Comparison of the presence of the IgG anti-SARS-CoV-2 antibodies between groups with mild to severe course of the disease

The 156 individuals included in the study were divided into two groups according to the severity of respiratory insufficiency. The criterion was the introduction of oxygen therapy:

- Group I included patients with a mild to moderate course of the disease – 136 individuals who required passive oxygen therapy with the use of nasal cannulas, simple face masks, and non-rebreather face masks; 66 individuals from this group completed the study.
- Group II included patients with a severe course of the disease – 18 individuals requiring high-flow oxygen therapy (with the use of HFNC-High Flow Nasal Cannula) or ventilator therapy; three individuals from this group completed the study.

The median concentration of the IgG antibodies in group II was 1,000 IU/mL, while in group I, the median concentration was 730.5 IU/mL, which constitutes a statistically significant difference ($p = 0.012$). In individuals with a severe course of the disease at months 3, 6, and 9 of the study, the median IgG antibody concentrations remained high at 1,371.1 IU/mL; 1,137.3 IU/mL; and 1,435.2 IU/mL, respectively. These differences were found to be statistically insignificant.

To compare, the median concentration of the IgG antibodies in group I at months 3, 6, and 9 of the study, was found to increase, constituting a statistically significant difference ($p < 0.001$), and amounted to 1,196.0 IU/mL; 1,225.5 IU/mL; and 1,265.1 IU/mL, respectively.

Table 1 presents changes in the concentrations of the IgG anti-SARS-CoV-2 antibodies between the groups of mildly, moderately, and severely ill individuals at three timepoints. The first timepoint was at 3 months after the onset of SARS-CoV-2 infection, as confirmed by the Real-Time PCR test, and next timepoints were at 6 and 9 months post infection.

These results indicate that the concentrations of the IgG anti-SARS-CoV-2 antibodies between the groups with mild to moderate disease course, and severe disease did not differ statistically significantly at any of the study's three timepoints.

Comparison of the presence of the IgG anti-SARS-CoV-2 antibodies in relation to sex of the patients

A comparison of the concentrations of the IgG anti-SARS-CoV-2 antibodies depending on the sex of the subjects found that the mean concentrations of the IgG antibodies were very similar between both sexes and amounted to 743.6 IU/mL (Q1-255.6 – Q3-998.2) and 743.4 IU/mL, respectively (Q1-253.5 – Q3-1005.9). Table 2 presents the differences and changes in the concentrations of the IgG anti-SARS-CoV-2 antibodies between females and males at three-time points – at 3, 6, and 9 months post infection with SARS-CoV-2.

A statistically significant increase in the level of the IgG anti-SARS-CoV-2 antibodies was found at 3 months post infection both in males – 1,239.6 IU/mL ($p < 0.001$) and in females – 1,288.5 IU/mL ($p = 0.005$). At 6 and 9 months post infection, the median concentration of IgG antibodies remained at a high level both in males and in females. At month 6 of the study, the concentration of antibodies in females was 1,222.6 IU/mL ($p < 0.001$), and in males – 1,222.4 ($p = 0.002$). At month 9 of the study, the concentration of antibodies in females was 1,385.9 IU/mL (p +0.027) and in males – 1,086.0 (p +0.034). Concentrations of the IgG anti-SARS-CoV-2 antibodies in males and females were not statistically significant at any of the study's three timepoints.

Table 1. Comparison of the presence of anti-SARS-CoV-2 antibodies in the IgG class between the groups of individuals with mild or moderate, and severe courses of the disease

Timepoint[1]		Group I Severe course of the disease	Group II Mild or moderate course of the disease	*P*
3	*N* Median concentration [25%,75%]	18 1,371.1[2] [740.1; 1508.1]	138 1,196.0[2] [725.9; 1470.4]	0.391
6	*N* Median concentration [25%,75%]	5 1,137.3[2] [1082.1; 1649.1]	91 1,225.5[2] [663.8; 1445.0]	0.542
9	*N* Median concentration [25%, 75%]	3 1,435.2[2] [1402.9; 1557.4]	66 1,265.1[2] [856.9; 1631.8]	0.453

[1] Months; [2] IU/mL

Table 2. Comparison of the presence of anti-SARS-CoV-2 antibodies in the IgG class in individuals depending on their sex

Timepoint[1]		Males	Females	*P*
3	*N* Median concentrations [25%,75%]	99 1,239.6[2] [720.2;1510.9]	57 1,288.5[2] [746.6;1450.1]	0.938
6	*N* Median concentrations [25%,75%]	66 1,222.6[2] [728.1;1480.8]	30 1,222.4[2] [725.1;1395.5]	0.816
9	*N* Median concentrations [25%,75%]	46 1,385.9[2] [972.9;1667.7]	23 1,086.0[2] [833.1;1561.7]	0.302

[1] Months; [2] IU/mL

Discussion

Our study shows that for individuals with a severe course of the disease the average concentration of the IgG class antibodies was slightly higher than in the group of individuals with a mild disease course. This difference was the highest at 9 months post infection, but it was only 170.1 IU/mL. The study findings suggest that humoral response developing as a result of infection depends on the severity of the condition. However, the conducted analysis does not show whether a high titre of the IgG class antibodies guarantees protection against subsequent infections. Studies conducted on macaques, as well as epidemiological studies into Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) infections, show that the presence of the IgG class anti-SARS-CoV-2 antibodies protects individuals from re-infection with SARS-CoV-2 [18–20].

The analysis conducted in this study, involving 18 individuals with a severe course and 138 individuals with a mild course of the disease, does not allow us to draw such far-reaching conclusions, as the period of observation of the convalescents was too short. Other researchers studying the efficacy of serological tests to assess the risk of re-infection, also believe that the presence of IgG antibodies may not be consistent with long-term immunity [18].

The results of the present study allow for the conclusion that individuals with a severe course of COVID-19 have slightly higher concentrations of immunoglobulins than individuals with a mild course. Similar conclusions were reached by scientists who analysed the concentration of IgG anti-SARS-CoV-2 antibodies [1]. They showed that virus-specific antibody titres were elevated in individuals with severe COVID-19 in comparison to asymptomatic individuals or those with a mild course of the disease [1].

These reports raise concerns about the effectiveness of humoral response in the course of infection and its evaluation as an indicator of groups at risk of re-infection. Another large retrospective study, which examined 38 serological tests, analysing IgG and IgM levels, indicated the validity of conducting serological tests only to differentiate between active and past infection with SARS-CoV-2 [21]. The suggestion that the quality rather than the quantity of antibodies may predict the outcome of infection was made in a recent report that used a panel of serological tests in 22 individuals with COVID-19 [10]. The titre of antibodies was higher in 10 individuals who died as a result of the infection than in 12 convalescents [10]. The study showed that the individuals who suffered a fatal outcome of the disease had an increased percentage of antibodies that stimulate phagocytes and neutrophils and a decreased level of antibodies that activate natural killer cells and recruit the complement [10]. The convalescents, on the other hand, had an increased concentration of antibodies stimulating natural killer cells and the complement system [10]. This study also showed that the survivors had higher titres of S-specific IgM and IgA1 antibodies against SARS-CoV-2, while in fatal cases an increase in titres of IgM and IgA1 antibodies targeting the N protein of the virus was observed [10].

It should be taken into consideration that humoral response is not the only mechanism contributing to the acquisition of long-term immunity in the event of COVID-19 infection. An enhanced T-cell response is described for most SARS-CoV-2 infections as the body's primary response to ongoing infection [22–24]. Melgaco et al., in their in vitro model, showed that infection of Peripheral Blood Mononuclear Cells (PBMC cells) with SARS-CoV-2 activated CD4+ memory cells that guarantee immunity [25]. Scientists point out that T cells play the main role in achieving immunity to infection with SARS-CoV-2. Therefore, analysing exclusively the parameters of humoral immunity in the assessment of re-infection is an inappropriate and unjustified approach. Other researchers found that members of the Bcl-2 family had modulated in the T cells of COVID-19 patients. More importantly, they demonstrated that the pan-caspase inhibitor, Q-VD, prevented T cell death by apoptosis and enhanced Th1 transcripts. Altogether, these results are compatible with a model in which T-cell apoptosis accounts for T lymphopaenia in individuals with severe COVID-19. Therefore, a strategy aimed at blocking caspase activation could be beneficial for preventing immunodeficiency in COVID-19 patients [26].

Our study did not show any significant differences in IgG anti-SARS-CoV-2 antibody concentrations between the sexes. It was shown that in both males and females, the median IgG antibody concentration was very similar – 743.6 IU/mL and 743.4 IU/mL, respectively. Both males and females showed a significant increase in IgG anti-SARS-CoV-2 antibodies during the 9-month observation period, but no significant differences were observed between the sexes. Similar results were obtained by Ishaq SE et al. who analysed the concentrations of IgG and IgM anti-SARS-Cov-2 antibodies in 383 males and 344 females [27]. The results showed that there was no significant difference in the production of both IgM and IgG in males in comparison to females [27]. The study of

489 convalescents did not show any differences between the IgG and IgM class anti-SARS-CoV-2 antibodies in males compared to females [28]. On the other hand, numerous studies of seroconversion of anti-SARS-CoV-2 antibodies indicate that age significantly affects the production of IgG antibodies [28–30]. In our study, significant differences based on age were observed at 3 months post infection. In the group of individuals over 60 years old, the concentration of the antibodies was 860.2 IU/mL and it was much lower than in the individuals at the age below 60, where the level of the antibodies was found to be 1,362.4 IU/mL. At 6 and 9 months post infection, the concentrations of the antibodies remained at a high level, and was comparable in both groups. The results of the present study are consistent with the current theory that the immune system of the elderly is less efficient, which is why the elderly are at a higher risk of severe course of infections. As regards the aging process, Andre et al. showed that COVID-19-infected patients presented with lymphopaenia, which was reported as being related to abnormal programmed cell death. Their findings demonstrated that individuals with high levels of CD4 T-cell apoptosis and CXCL10 have a poor ability to build an efficient anti-S response. Detailed T cell responses could be developed as their S-transfected cells (S-Flow) assays and CXCL10 concentration measurement provide a helpful indication [31].

Another aim of our study was to assess the effectiveness of vaccines in the synthesis of IgG SARS-CoV-2 specific antibodies. Korang, Hall, Baden, et al. proved in their publications that the two mRNA vaccines available on the market – Pfizer/BioNTech, Moderna, and the two vector vaccines – AstraZeneca and Johnson & Johnson – reduced the risk of the severe course of COVID-19 and the number of hospitalisations as well as morbidity associated with the disease [32–34]. The relationship between the presence of IgG antibodies and a significantly reduced risk of SARS-CoV-2 re-infection has also been documented [35]. The antibodies produced as a result of viral infection or vaccination can improve humoral response and provide protection against re-infection, which can even last for life [36]. Our study demonstrates the effectiveness of vaccines in the development of the humoral immunity in individuals after SARS-CoV-2 infection. In both study groups, at study point 0, there were comparable antibody levels in both vaccinated and unvaccinated individuals: 650.7 AU/mL and 747.9 AU/mL, respectively. At 3 months post infection, there was a rapid increase in the concentration of antibodies in the group of vaccinated individuals, up to 1,373.7 AU/mL. In the unvaccinated group, the antibody concentration was 830.8 AU/mL. The IgG antibody level in the vaccinated group remained at 1,291.5 AU/mL at 6 months post infection, while in the unvaccinated group, the antibody concentration decreased rapidly to 298.1 AU/mL. Nine months after the onset of the infection, the level of IgG antibodies in the group of vaccinated individuals was 1,430.9 AU/mL, while in the unvaccinated individuals it was 661.3 AU/mL. The mean antibody level difference between the vaccinated and unvaccinated subjects was 769.6 AU/mL at the final stage of the study. The evaluation showed that the vaccines were not only associated with faster immunity acquisition, but they were also responsible for maintaining higher concentrations of IgG antibodies for a longer period of time. The results obtained in the present study are consistent with the findings published by other researchers and confirm the effectiveness of vaccines in antibody production. In a study by Earle et al., a strong correlation was observed between the titre of neutralising antibodies and the titre of IgG antibodies against the Spike protein and the effectiveness of the vaccine despite geographically diverse study populations [37]. Garcia-Beltran et al., in a study of 239 vaccinated individuals, showed the effect of the vaccine, in particular the booster dose, on enhancing the cross-reactivity of the neutralising antibody response [38]. Another published study, involving 33 healthy adult participants, found that after receiving the second dose of the vaccine, high levels of binding and neutralising IgG antibodies were present for 180 days post vaccination, providing effective protection against re-infection with SARS-CoV-2 [39].

The study showed that taking the vaccine significantly affected the production of anti-SARS-CoV-2 IgG antibodies in virtually every analysed group. The analysis of the results also revealed that in severely and moderately ill people, vaccinations additionally stimulated humoral response, despite their immunodeficiency and poor overall condition. These analyses validate the effectiveness of vaccinations in preventing the severe course of COVID-19 and also show that even in patients who have recovered from the infection, the vaccines enhance the production of IgG antibodies and facilitate the development of secondary immune response.

The findings also suggest that people who were severely and moderately ill with COVID-19 showed a greater motivation to vaccinate compared to people with mild symptoms. In severely and moderately ill patients, at 6 and 9 months post infection, the number of vaccinated patients was 78% and 85%, respectively. Unfortunately, this shows that the main factor encouraging people to get vaccinated is the severity of infection.

However, studies analysing the concentration of IgG antibodies in convalescents and patients recovering from COVID-19, who were given the mRNA vaccine, showed that hybrid immunity resulted in a better antibody response, and people who had no previous infection would need a booster dose earlier than infected individuals [11]. We observed a rapid decrease in antibody titre in the group of unvaccinated individuals at month 6 of the follow-up, from 830.8 AU/mL (month 3) to 298.1 AU/mL. Such results have not yet been reported in the available literature. This fact can be explained by the effects of immunosuppressive treatment in this study group. Undoubtedly, there is a need for further observational studies to thoroughly understand all the mechanisms of acquiring immunity after SARS-CoV-2 infection. On the basis of the results of the present study and the data in the available literature, it cannot be concluded whether anti-SARS-CoV-2 antibodies created post-vaccination are a reliable indicator of the effectiveness of preventive vaccinations. Undoubtedly, in the development of long-term immunity, the mechanisms of cellular immunity should also be taken into account. It is also necessary to conduct further population studies in the long term to be able to assess the effectiveness of vaccinations.

Conclusions

The concentration of IgG anti-SARS-CoV-2 antibodies in the group of patients with severe signs of SARS-CoV-2 infection is significantly higher in comparison to the group of individuals with mild and moderate course of the disease. However, the analysis of antibody concentration did not allow us to draw any conclusions about the severity of the course of the disease. The level of IgG class anti-SARS-CoV-2 antibodies is not a parameter which is dependent on the sex of affected individuals, but rather on their age. In individuals over the age of 60 years old, the production of IgG anti-SARS-CoV-2 antibodies is lower. In vaccinated individuals in this age group, the level of IgG anti-SARS-CoV-2 antibodies is higher than in unvaccinated individuals, however, the assessment of the titre of IgG anti-SARS-CoV-2 antibodies alone should not be a determinant of the validity of vaccination.

The assessment of the titre of the IgG anti-SARS-CoV-2 antibodies is not a parameter determining the effectiveness of the vaccination but rather an indicator of past infection. Also, this parameter is insufficient for the assessment of the risk of re-infection, as well as the effectiveness of vaccination.

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