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Comparison of First and 21st Day anti SARS-CoV-2 anti-spike IgM and IgG Responses

İlk ve 21. Gün anti SARS-CoV-2 anti-spike IgM ve IgG Yanıtlarının Karşılaştırılması

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Abstract

Objective: There is no definitive information yet about antibody kinetics produced in response to coronavirus disease-2019 (COVID-19) infection. It is essential to know the antibody levels in different patient groups. Our study compared the immunoglobulin M (IgM) and immunoglobulin G (IgG) type antibody levels developed against COVID-19 infection by age groups and first-time complaints.

Materials and Methods: IgM and IgG levels were investigated on the day of diagnosis and on the 21st day on serum samples with a point-of-care tests device in ninety-four COVID-19 patients. Antibody responses were evaluated according to age groups and clinical complaints.

Results: First day IgM levels than 21st day and 21st day IgG levels than the first day were significantly higher ($p=0.006$, $p<0.001$, respectively). IgG on the first day and IgM on the 21st day was positive (>1). While IgG type antibody response was dominant in children, it was found that a robust antibody response occurred in young adults and over 65 years of age.

Conclusion: Anti-spike severe acute respiratory syndrome-coronavirus-2 IgM antibodies remain positive for more extended periods, unlike known infectious agents, and measuring positive IgG values on the first day is insignificant in terms of protection against infection and appears specific to COVID-19. While IgG type antibodies dominate children, strong IgG and IgM type responses can be detected in young adults and the elderly. Different antibody responses may develop according to clinical findings.

Keywords: SARS-CoV-2, COVID-19 virus, viral antibodies, point-of-care testing

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonuna yanıt olarak üretilen antikor kinetikleri hakkında henüz kesin bilgi yoktur. Farklı hasta gruplarında antikor seviyelerinin bilinmesi hayatidir. Çalışmamızda, COVID-19 enfeksiyonuna karşı geliştirilen immünoglobulin M (IgM) ve immünoglobulin G (IgG) tipi antikor düzeylerinin yaş grupları ve ilk şikayetlere göre karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Doksan dört COVID-19 hastasında tanı günü ve 21. günde hasta-başı test cihazı ile serum örneklerinde IgM ve IgG düzeyleri incelenmiştir. Antikor yanıtları yaş gruplarına ve klinik şikayetlere göre değerlendirilmiştir.

Bulgular: İlk gün IgM düzeyleri 21. günden ve 21. gün IgG düzeyleri birinci günden anlamlı olarak yüksekti (sırasıyla, $p=0.006$, $p<0.001$). İlk gün IgG ve 21. gün IgM düzeyleri pozitif saptanmıştır (>1). Çocuklarda IgG tipi antikor yanıtı baskın olurken, 65 yaş üstü ve genç erişkinlerde güçlü bir antikor yanıtının oluştuğu gözlenmiştir.

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Sonuç: Başak proteinine karşı oluşan şiddetli akut solunum yolu sendromu-koronavirüsü-2 IgM antikorları, Sars-Cov-2'ye özgün olmak ile birlikte, ilk günden IgG antikorlarının oluşmasına rağmen, enfeksiyona karşı tam bir koruma sağlamıyor gibi görünmektedir. IgG tipi antikorlar çocukluk çağında baskınken, genç yetişkinlerde ve yaşlılarda güçlü IgG ve IgM tipi yanıtlar tespit edilebilmektedir. Klinik bulgulara göre farklı antikor yanıtları gelişebilir.

Anahtar Kelimeler: SARS-CoV-2, COVID-19 virüsü, viral antikorlar, hasta-başı test

Introduction

Apart from promising clinical trials, no effective treatment has yet resolved the pandemic caused by coronavirus disease-2019 (COVID-19) infection (1). Knowing how the defense system will respond against COVID-19 and whether this response will be sufficient to prevent infection plays a crucial role in our fight against the pandemic. Antibodies are vital in preventing infections in the defense system (2). It is hoped that antibodies developed against COVID-19 will also be protective, to antibodies developed against other infectious agents. In those with COVID-19 infections immunoglobulin G (IgG)-type antibodies are produced that target the viral nucleocapsid (N), spike (S), and spike S receptor binding site (RBD), which are valuable for inactivating the virus (3). It has been reported that these antibody levels are low in those with mild disease and high in those with severe disease and decrease in the long term (4,5). In this context, all vaccination studies provide sufficient levels of antibodies in the circulation against the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) factor, which is unknown yet. Although it does not cover deveoping countries, vaccination practices that are becoming widespread are promising for humanity (6). It has been detected at least one specific antibody type against SARS-CoV-2 in 30% of patients one week after the onset of COVID-19, 72.2% after two weeks, in 91.4% after three weeks and in 96% at the end of the 5th week (7). As the coronavirus is becoming a pandemic, interest in antibody testing has increased in terms of how widespread the infection has advanced and detecting individuals who may be immune (8). Considering the various clinical findings of COVID-19 and the false-negative results of reverse transcription-polymerase chain reaction (RT-PCR) tests, antibody tests have come to the fore, especially in patients whose swab samples are taken after the fifth day when the sensitivity for RT-PCR is reduced (9,10). Although IgG and IgA reach higher levels later, IgG, in particular, circulates at higher levels for a more extended time (11). There are also point-of-care tests (POCT) using disposable devices called lateral flow assays, which are inexpensive and relatively fast analyses (12). Although the sensitivity and specificity of POCT measurements are lower than that of immunoassays, they are used as a practical method in examining community immunity and determining the level of exposure to SARS-CoV-2 (13). However, it should be known that the defense response to COVID-19 does not consist solely of antibody synthesis (14). It is thought that T and B-cells are effective against pathogens (10). The role of T-cell memory in body defense against COVID-19 has been demonstrated in laboratory tests, and the cross-reactivity of T-cell responses to other coronavirus infections may explain changes in the clinical severity of COVID-19 (15). However, routine, reproducible, and comparable evaluations of T-cell responses are impossible (16). Besides, protective antibody responses can achieve virus neutralization without the need for T-cell defense (17). Virus neutralizing antibody levels are essential for protection from COVID-19 infection, and scientific data on the kinetics of antibody responses are needed (18). Data models indicate that antibody responses that develop after overcoming infection provide protection against relapse for about one year (19). However, there is no absolute proof yet about the level of protective antibody responses. Additionally, we do not have definite information regarding antibody kinetics developing in different patient groups. Our motivation to materialize this study was to analyze antibody responses developed according to age ranges and clinical complaints and examine the predicted level of protection by examining the IgG values on the 21st day.

Materials and Methods

Subjects

Ninety-four out of one hundred and thirty-six unvaccinated patients, at different ages and with different admission complaints, whose SARS-CoV-2 genetic material was detected by RT-PCR in the nasal swab sample were included in the study (Table 1). Thirty-two patients using drugs or having diseases that cause immunosuppression, with chronic diseases, organ transplant or failure patients, pregnant women, have a different infection simultaneously, and diagnosed with malnutrition were excluded. Ten patients whose SARS-CoV-2 test result remained positive after the RT-PCR was repeated on the 21st day were excluded from the study. Hydroxychloroquine sulfate 200 mg oral treatment was started in all patients except <18 ages, 8 times in the first two days and 5 times in the following days, as compliance with the Ministry of Health guidelines. No patient was hospitalized. All patients volunteered for the study by signing the informed consent form. After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval

was obtained from the Afyonkarahisar Health Sciences University School of Medicine ethical board with a 2021/3 number (date: 05.03.2021).

Study Design

Anti-spike protein IgG and IgM analysis were performed on the day of diagnosis and on the 21st day of diagnosis of patients diagnosed with COVID-19 between Jan 4, 2021, and Feb 5, 2021. Evaluations were made by forming separate groups according to the first examination complaints and age groups. Blood samples taken from the patients were centrifuged at 1.500 G for 15 min in tubes without additives to obtain serum samples, and analyses were performed. Since COVID-19 antibodies that are likely to develop in patients over time are being investigated, SARS-CoV-2 anti-spike protein IgG and IgM tests were performed on the day of diagnosis and 21 days after diagnosis. The tests were analyzed using the Standard F2400, CE-approved rapid POCT device (S.D. Biosensor, Gyeonggi-do, Republic of Korea), with the lateral flow immunoassay method and card tests containing two-dimensional square code under the manufacturer's product insert. Standard F COVID-19 IgM/IgG Combo FIA (S.D. Biosensor, Gyeonggi-do, Republic of Korea) fluorescent immunoassay reagent was used for the qualitative detection of specific antibodies to SARS-CoV-2 present in human serum. The sensitivity for IgM was 71.8% and 91.7% for IgG. Specificity for IgM is 100% and 96.7% for IgG. Sensitivity was 94.41% [95% confidence interval (CI), 89.27%-97.55%], and specificity was 90.62% (95% CI, 85.01%-94.66%). The results were reported as calculated luminescence units per mL (A.U./mL); values ≥1.00 AU/mL are considered positive, while values <1.00 AU/mL are considered negative, according to the manufacturer. Antibody units were in ng/mL.

Statistical Analysis

Whether the data distributed normally was investigated using Excel (Microsoft Inc, Redmont, Washington, USA). Paired sample t-test was used to compare parametric group means, and the Wilcoxon test was used to compare the non-parametric ones. Antibody responses expected to change over time were analyzed using linear regression analysis. We summarized variables as mean ± standard error, mean ± standard deviation. P-values below 0.05 were considered significant. Statistical analyses were assessed via SPSS 16 statistical software (IBM Inc, Illinois, USA).

Table 1. Demographic data of patients included and excluded from the study.

Age	Male	Female	Excluded patients
0-18	3	2	2
19-35	7	6	8
36-50	10	10	6
51-65	14	13	9
65+	15	14	17
Total	49	45	42

Results

Sixty-one percent of the cases were male, and the median age was forty-one. There was no difference in age between the genders (p=0.276). The mean IgM titer on the first day was found to be significantly lower than that on the 21st day (p=0.006). However, the mean of the IgG measurements on the 21st day was significantly higher than on the first day (p<0.001). When the linear regression analysis was performed, a statistically significant relationship was found between the IgM values on the first day and the IgG values on the 21st day (r^2=0.794, p=0.026). The mean and standard errors of the IgG antibody levels on the 21st day, which are suggestive in terms of protection, and the first day IgM antibody levels in the first response to infection were 9.60±0.59 and 10.19±2.59, respectively (Table 2). The IgM levels on the first day were significantly higher in the patients who presented with fatigue and postnasal drip compared to the other groups (p=0.012, mean: 19.82 and p=0.023, mean: 16.91, respectively). IgG levels on 21st day in patients with fever were significantly higher (p=0.031 and mean: 17.0). Symptoms and antibody titers are shown in Table 3 and depicted in Figure 1. The first day IgM levels were found to be significantly lower in the 0-18 age range and 51-65 age range compared to the other age groups (p=0.014, mean: 0.99 and p=0.036, mean: 4.31, respectively). According to age ranges, no significant difference was found in IgG levels on the 21st day (Table 4).

Discussion

Our study results determined significant increases in IgM values on the day of diagnosis of COVID- 19 and IgG values on day 21. Although there is no finalized data, by taking the pooled results for IgG, IgM, IgA, total antibody levels, and combined IgG/IgM, it was noted that the highest antibody measurements were detected in the third week of symptoms (20). Considering the overall response to infection and the immune response to upper respiratory viral agents, IgM values also showed high levels in the early period in COVID-19 patients. It has been reported that despite the low plasma titers, antibodies against three different epitopes on the RBD neutralize the virus with semi-maximal inhibitory concentrations (IC50 values) as low as 2 ng mL^{-1} and short-term antibody responses against SARS-CoV-2 inactivated in approximately 40 days, especially IgM levels (21). According to our study results, although there was a significant decrease in IgM responses

on the 21st day, the average IgM levels were cilically significant even on the 21st day. This finding revealed that the immune response to COVID-19 was not similar to that of known respiratory viruses or other pathogens in terms of IgM. It has been suggested that the IgG responses against the SARS-CoV-2 spike protein lasted for months and even show strong IgG responses against re-infection (22). Our study suggested that day 21 IgG values were high and it supported the idea of robust immune response against COVID-19, although it did not last long. The positive detection of IgG values on the first day seem to be specific to COVID-19.

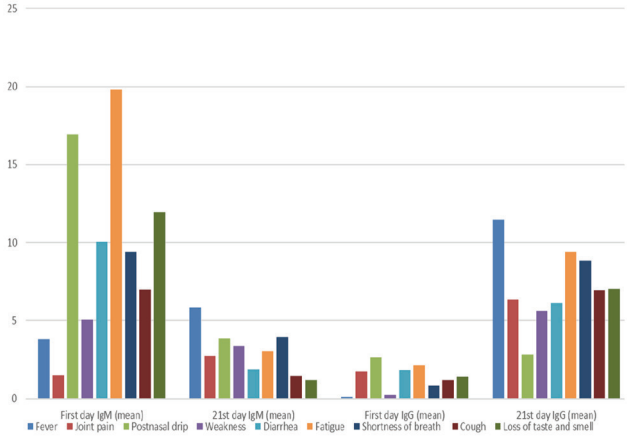

Figure 1. Signs, symptoms and the mean values of first and 21st day IgM and IgG measurements.

The reason for the high IgG response in patients presenting with fever at the first examination could be considered a sign that the disease will show a more severe course with a high fever. However, this hypothesis needs confirmation. Despite the relatively low IgM responses developed on the first day in COVID-19 patients admitted to the clinic with high fever and joint pain, there remains to be an explanation for the high IgG levels on the 21st day. A study stated that although higher IgG responses were found in those who experienced the loss of taste and smell, there was no difference between these patients and healthy individuals in terms of clinical course (23). We could not find an analysis comparing antibody responses according to the first examination findings. A mechanistic explanation about the patient's clinical course can be obtained by evaluating the antibody responses and the examination findings.

Studies have shown that COVID-19 leads very mild symptoms in the pediatric age group and that very few patients required mechanical ventilation (24). It has been shown that the antibody response that developed against COVID-19 in children was of the IgG type ant its levels were found be similar to those of adults (25). Similarly, our finding of low IgM values on the first

Table 2. Descriptive data of age and antibody levels.

	Age	First day IgM ng/mL	21st day IgM ng/mL	First day IgG ng/mL	21st day IgG ng/mL
Mean	41.193	10.194	2.691	1.432	9.600
Standard error	2.007	2.585	0.593	0.361	0.587
Median	41.000	0.900	0.835	0.090	12.000
Minimum	5.000	0.000	0.000	0.000	0.010
Maximum	86.000	97.430	49.000	14.550	18.200
p-value		**0.006**		**<0.001**	

IgM: Immunoglobulin M, IgG: Immunoglobulin G

Table 3. The mean and median values of first day IgM and 21st day IgG measurements according to clinical complaints.

Complaint	First day IgM (mean) ng/mL	21st day IgM (mean) ng/mL	p-value	First day IgG (mean) ng/mL	21st day IgG (mean) ng/mL	p-value
Fever	3.81	5.82	0.324	0.1	11.45	**0.003**
Joint pain	1.51	2.73	0.211	1.76	6.37	**0.028**
Postnasal drip	16.91	3.88	**0.016**	2.66	2.81	0.962
Weakness	5.05	3.4	0.098	0.23	5.64	**0.014**
Diarrhea	10.04	1.9	**0.012**	1.82	6.12	**0.037**
Fatigue	19.82	3.04	**0.01**	2.13	9.42	**0.027**
Shortness of breath	9.42	3.96	0.064	0.86	8.86	**0.001**
Cough	7.01	1.44	**0.041**	1.19	6.94	**0.011**
Loss of taste and smell	11.92	1.2	**0.005**	1.41	7.03	**0.004**

IgM: Immunoglobulin M, IgG: Immunoglobulin G

Table 4. The mean values of first-day IgM and 21st day IgG measurements according to age groups.

Age	First day IgM (mean) ng/mL	21st day IgM (mean) ng/mL	p-value	First day IgG (mean) ng/mL	21st day IgG (mean) ng/mL	p-value
0-18	0.99	0.91	0.464	8.87	6.13	0.109
19-35	12.73	8.62	**0.038**	8.53	5.29	**0.049**
36-50	10.92	7.23	**0.047**	10.36	6.38	0.041
51-65	4.31	3.24	0.136	8.21	7.16	0.219
65+	11.39	9.76	0.067	10.6	8.22	0.178

IgM: Immunoglobulin M, IgG: Immunoglobulin G

day under 18 years of age might be related to the mild course of infection in children. However, measuring high IgG values on the 21st day in the same group may show that the immune system in children is as effective as adults in recognizing microbiological factors and providing protective antibody synthesis. A different hypothesis indicated that human coronaviruses infection is common in childhood, but the prevalence of these viruses may vary from year to year (26). As we age, the immune response of the host change (27). Therefore, the ability to fight respiratory infections and the antibody responses to vaccines might decrease (28). Besides, it has been reported that although IgA, IgM, and IgG type antibodies were detected against both nucleocapsid and spike protein in adults, only IgG type antibody was observed against spike protein in children, and neutralizing antibody responses were independent of age and adulthood (29). Although our results are generally in line with the literature, high antibody responses in both IgM and IgG types detected in young adults and over 65 years age are considerably important. Finally, we should mention that this study was conducted at a time when COVID-19 antibody levels were not yet ready to be studied with immunoassay devices. Although studies conducted with immunoassays methods should be more valuable in terms of sensitivity and specificity than POCT devices. Those devices necessitates long sample preparation and test run times and have high costs. When POCT devices are used for rapid diagnosis and screening in diseases that affect many people, such as the COVID-19, they are valuable in terms of public health.

Study Limitations

We could not assess the antibody levels in patients for longer periods. Since we did not make any interpretation in terms of the sensitivity of RT-PCR tests, we also could not exclude the patients with false positive results. Also, another limitation of our study was the significant difference in the number of patients in different age groups. Studies with similar numbers of patients in the same age groups may be more enlightening.

Conclusion

We have shown that anti-spike SARS-CoV-2 IgM antibodies remain positive for more extended periods than those of known infectious agents, and clinical findings should be evaluated carefully. However, positive IgG values on the first day is also insignificant in terms of protection against infection and appears to be specific to COVID-19. The significantly lower IgM values in patients aged 51-65 years may be due to biological variation in patients in this age group. Or, if patients have previously had an asymptomatic or hospital-independent COVID-19 infection (which is highly probable in patients with COVID-19 in this age group), recovered patients may show lower IgM responses possibly due to stronger immune response. Antibody titers may differ between patients according to signs and symptoms of the disease and different age groups. While anti-spike IgG antibodies against COVID-19 showed a significant increase in childhood, same high levels of anit-spike protein IgM were not expected. Additionally, although POCT devices are less sensitive and although they are more sensitive than immunoassay methods, they can significantly alleviate the burden on the global health system in COVID-19 pandemic, which presents racing against time for rapid diagnosis and screening.

Ethics

Ethics Committee Approval: After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval was obtained from the Afyonkarahisar Health Sciences University School of Medicine ethical board with a 2021/3 number (date: 05.03.2021).

Informed Consent: The patients volunteered for the study by signing the informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E.D., A.B., E.M., M.D., A.G., Design: M.E.D., A.B., E.M., M.D., A.G., Data Collection or Processing: M.E.D., A.B., E.M., M.D., A.G., Analysis or Interpretation: M.E.D., A.B., E.M., M.D., A.G., Literature

Search: M.E.D., A.B., E.M., M.D., A.G., Writing: M.E.D., A.B., E.M., M.D., A.G.

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